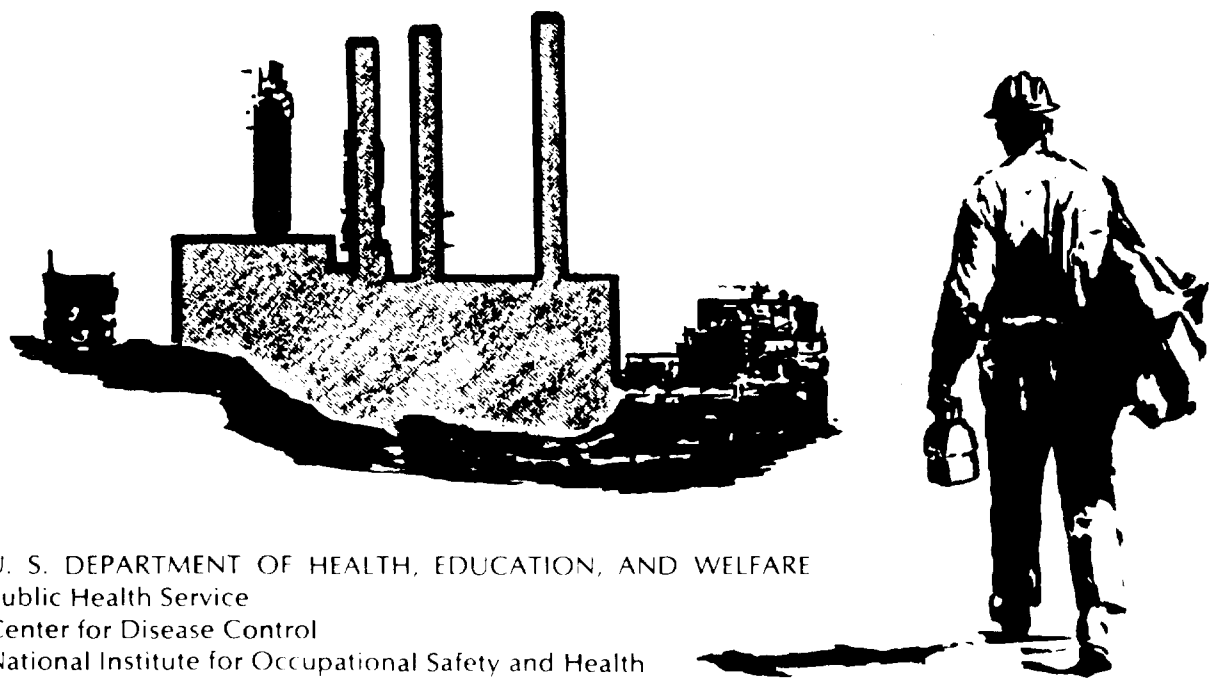
# NIOSH

# CRITERIA FOR A RECOMMENDED STANDARD....

## OCCUPATIONAL EXPOSURE TO

# BENZYL CHLORIDE



U. S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

# criteria for a recommended standard....

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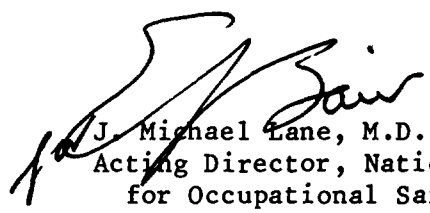
# PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

The contributions to this document on benzyl chloride by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the Society of Toxicology, the American Industrial Hygiene Association, and the American Academy of Occupational Medicine, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views and conclusions expressed in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages v and vi.



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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for benzyl chloride. Terence M. Grady of this Division served as criteria manager. Equitable Environmental Health, Inc. (EEH) developed the basic information for consideration by NIOSH staff and consultants under contract CDC 210-77-0148.

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# I. RECOMMENDATIONS FOR A BENZYL CHLORIDE STANDARD

NIOSH recommends that employee exposure to benzyl chloride in the workplace be controlled by adherence to the following sections. The recommended standard is designed to protect the health and provide for the safety of employees for up to a 10-hour workshift, 40-hour workweek, over a working lifetime. Compliance with all sections of the recommended standard should prevent adverse effects of exposure to benzyl chloride on the health of employees and provide for their safety. The standard is measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. Although NIOSH considers the workplace environmental limit to be a safe level based on current information, the employer should regard it as the upper boundary of exposure and make every effort to maintain the exposure as low as is technically feasible. The criteria and standard will be reviewed and revised as necessary.

These criteria and the recommended standard apply to exposure of employees to the chlorinated hydrocarbon $C_6H_5CH_2Cl$, hereinafter referred to as "benzyl chloride" in occupational environments. Synonyms for benzyl chloride include alpha-chlorotoluene, (chloromethyl) benzene, omega-chlorotoluene, and chlorophenylmethane. The major use of benzyl chloride is as an intermediate in organic synthesis. It has also been used as a high-pressure lubricant and was proposed for use as a war gas.

Benzyl chloride vapor and aerosol may irritate the skin, eyes, nose, and upper respiratory tract. The irritant properties provide sufficient warning such that employees do not voluntarily remain in areas of high (50 mg/cu m) concentrations. The odor of benzyl chloride, however, does not provide adequate warning of concentrations that may cause eye irritation. Direct contact of liquid benzyl chloride with the skin can cause burns. The recommended standard is designed to safeguard workers occupationally exposed to benzyl chloride from irritation of the eyes, skin, or mucous membranes and to reduce the risk of long-term systemic effects.

"Occupational exposure" to benzyl chloride is defined as work in any area where benzyl chloride is manufactured, processed, stored, handled, or used. Compliance with all sections of the recommended standard is required where there is occupational exposure to benzyl chloride. If benzyl chloride is handled or stored only in sealed, intact containers, eg, during shipment or storage, the recommended standard, except for Sections 3, 5(a), and 6(e), shall not apply. If exposure to other chemicals also occurs, provisions of any applicable standards for such other chemicals shall also apply.

Section 1 - Environmental (Workplace Air)

(a) Concentration

Exposure to benzyl chloride shall be controlled so that no employee is exposed to benzyl chloride at a concentration greater than 5.0 milligrams per cubic meter (mg/cu m) determined as a ceiling concentration during any 15-minute sampling period.

(b) Sampling and Analysis

Workplace air samples shall be collected and analyzed as described in Appendix I, or by any method shown to be at least equivalent in precision, sensitivity, and accuracy.

Section 2 - Medical

Medical surveillance shall be made available as outlined below to all employees occupationally exposed to benzyl chloride.

(a) Preplacement medical examinations shall include at least:

(1) Comprehensive medical and work histories, with special emphasis directed to disorders of the respiratory system, skin, and eyes.

(2) A physical examination, with particular emphasis given to the respiratory system, skin, and eyes.

(3) A judgment of the worker's ability to use a positive pressure respirator.

(4) Specific clinical tests including at least a 14- x 17-inch posteroanterior chest roentgenogram, and tests of pulmonary function including forced expiratory volume during the 1st second ($FEV_1$) and forced vital capacity (FVC).

(b) Periodic examinations shall be made available at least annually to all employees occupationally exposed to benzyl chloride. These examinations shall include at least:

(1) Interim medical and work histories.

(2) Physical examination as described in (a)(2) and (a)(4) of this section, with the exception of the chest roentgenogram.

(c) Applicants or employees found during examinations to have medical conditions, such as emphysema, that could be aggravated directly or

indirectly by exposure to benzyl chloride shall be counseled as to the possibly increased risk of impairment of their health as a result of working with this substance.

(d) In the event of irritation or illness known or suspected to be due to exposure to benzyl chloride, appropriate medical services shall be made available.

(e) In an emergency involving massive exposure to benzyl chloride, either by inhalation or dermal contact, immediate medical attention and appropriate followup medical care shall be provided.

(f) Pertinent medical records shall be maintained for all employees occupationally exposed to benzyl chloride. Such records shall be kept for at least 30 years after termination of employment. Records of environmental exposures applicable to an employee shall be included with the employee's medical records. These records shall be made available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employer, and of the employee or former employee.

Section 3 - Labeling and Posting

All warning signs shall be printed both in English and in the predominant language of non-English-reading workers. Workers unable to read labels and posted signs shall receive information regarding hazardous areas and shall be informed of the instructions printed on labels and signs.

(a) Labeling

The following warning label shall be affixed in a readily visible location on process equipment, storage tanks, containers, or other facilities used for benzyl chloride:

BENZYL CHLORIDE

WARNING!
HIGHLY IRRITATING TO SKIN AND EYES
HARMFUL IF INHALED
CAN BE FATAL IF SWALLOWED

Use only with adequate ventilation.
Keep containers closed when not in use.
Wash hands thoroughly before eating, drinking, smoking, or using toilet.

First aid: If inhaled, remove to fresh air. Give artificial respiration if needed. Get medical attention.

In case of skin or eye contact: Immediately wash skin thoroughly or flush eyes with copious amounts of water. Get medical attention.

If swallowed: Induce vomiting immediately if patient is conscious. Get immediate medical attention.

(b) Posting

Areas in which benzyl chloride is present shall be posted with signs reading:

BENZYL CHLORIDE

WARNING!
HIGHLY IRRITATING TO SKIN AND EYES
HARMFUL IF INHALED
CAN BE FATAL IF SWALLOWED

Section 4 - Personal Protective Equipment and Clothing

(a) Eye and Face Protection

Safety glasses, chemical safety goggles, or face shields (20-cm minimum) with goggles shall be provided by the employer and shall be worn during any operation in which benzyl chloride may come in contact with the eyes (29 CFR 1910.133).

(b) Respiratory Protection

Engineering controls shall be used whenever needed to maintain airborne benzyl chloride concentrations at or below the recommended occupational exposure limits. Compliance with these limits by the use of respirators is permitted only during installation and testing of engineering controls, during performance of nonroutine maintenance or repair, when working in confined spaces, or during emergencies. When use of a respirator is permitted, it shall be selected and used in accordance with the following requirements:

(1) The employer shall ensure that no employee is exposed to benzyl chloride because of improper respirator selection, fit, use, or maintenance.

(2) The employer shall establish and enforce a respiratory protection program meeting the requirements of 29 CFR 1910.134.

(3) The employer shall provide respirators in accordance with Table I-1 and shall require that the employee use the respirator provided when necessary.

(4) Respiratory protective devices described in Table I-1 shall be those approved under the provisions of 30 CFR 11.

(5) Respirators specified for use in atmospheres of higher concentrations of benzyl chloride may be used in atmospheres of lower concentrations.

(6) The employer shall ensure that respirators are adequately cleaned and maintained and that employees are instructed and drilled, at least annually, in the proper use and testing for leakage of respirators assigned to them.

(7) Respirators shall be easily accessible and employees shall be informed of their location.

(c) Protective Clothing

Protective clothing shall be resistant to penetration by, and to the chemical action of, benzyl chloride. Additional protection, including gloves, bib-type aprons, boots, or overshoes, shall be provided for, and worn by, each employee wherever there may be direct contact with liquid benzyl chloride. Supplied-air hoods or suits resistant to penetration by benzyl chloride shall be worn when entering confined spaces, such as pits or storage tanks. In situations where heat stress is likely to occur, supplied-air suits, preferably cooled, are recommended. The employer shall ensure that all personal protective clothing is inspected regularly for defects and is maintained in a clean and satisfactory condition. Protective equipment suitable for emergency use shall be located at clearly identified stations outside the work area.

## Section 5 - Informing Employees of Hazards from Benzyl Chloride

(a) All new and present employees working with benzyl chloride shall be informed orally and in writing of the hazards, relevant signs and symptoms of exposure, appropriate emergency procedures, and proper conditions and precautions concerning safe use and handling of benzyl chloride. First-aid procedures shall be included. This information shall be readily available to all employees involved in the manufacture, use, transport, or storage of benzyl chloride and shall be posted in prominent positions within the workplace.

(b) Employers shall institute a continuing education program to ensure that all new and present employees subject to occupational exposure to

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR BENZYL CHLORIDE

| Concentration | Respirator Type Approved under Provisions of 30 CFR 11 |
|---|---|
| Less than or equal to 50 mg/cu m | (1) Supplied-air respirator with full facepiece, helmet, or hood<br>(2) Self-contained breathing apparatus with full facepiece |
| Less than or equal to 10,000 mg/cu m | (1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode<br>(2) Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure mode or with full facepiece, hood, or helmet operated in continuous-flow mode |
| Greater than 10,000 mg/cu m or emergency (entry into area of unknown concentration) | (1) Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode<br>(2) Combination respirator that includes Type C supplied-air respirator with full facepiece operated in pressure-demand or other positive pressure or continuous-flow mode and auxiliary self-contained breathing apparatus operated in pressure-demand or other positive pressure mode<br>(3) Supplied-air suits may be necessary |
| Firefighting | Self-contained breathing apparatus with full facepiece operated in pressure-demand or other positive pressure mode |

benzyl chloride have current knowledge of job hazards, maintenance procedures, cleanup methods, emergency procedures, and evacuation procedures. This program shall include at least:

Emergency procedures and drills.
Instruction in handling spills and leaks.
Decontamination procedures.
Location and use of firefighting equipment.
First-aid procedures, equipment location, and use.
Rescue procedures.
Confined space entry procedures.
Warning concerning inadequacy of odor as a means of detecting low concentrations that may cause eye irritation.

Such training shall be conducted at least annually, and records of such training shall be kept for at least 1 year.

(c) Information, as required, shall be recorded on the Material Safety Data Sheet shown in Appendix II, or on a similar form approved by the Occupational Safety and Health Administration, US Department of Labor.

Section 6 - Work Practices

(a) Emergency Procedures

For all work areas where there is a likelihood that emergencies may occur, the employer shall take all necessary steps to ensure that employees are instructed in, and follow, the procedures specified below and any other procedures appropriate to the specific operation or process.

(1) Emergency procedures shall include at least prearranged plans for:

(A) Immediate evacuation, transportation, and medical assistance for affected employees; this procedure should include alerting medical treatment facilities of the impending arrival of affected employees.

(B) Designation of medical receiving facilities.

(C) Reentry into areas where benzyl chloride leaks or spills have occurred for cleanup, decontamination, or maintenance purposes.

(2) Personal protective equipment and clothing as specified in Section 4 shall be used by trained personnel essential to emergency operations.

(3) Nonessential employees shall be evacuated from hazardous areas during emergencies. Perimeters of these areas shall be posted and secured.

(4) Only trained personnel shall shut off sources of benzyl chloride, and only those protected against the attendant hazards shall clean up spills, control and repair leaks, and fight fires.

(5) Firefighting procedures shall be established for areas where flammable materials are used with benzyl chloride. Chemical foam, carbon dioxide, dry chemicals, or water spray or fog shall be used for fighting fires in areas where benzyl chloride is present. Protective equipment and clothing appropriate to the hazard shall be worn by all personnel in the area until concentrations of airborne benzyl chloride have been demonstrated by monitoring to be at or below the recommended occupational exposure limit.

(6) Showers, eyewash fountains, and washroom facilities shall be provided and be readily accessible to workers in all areas where skin or eye contact with liquid benzyl chloride is likely. If liquid benzyl chloride is splashed on the clothing or skin, contaminated clothing shall be promptly removed and the skin washed thoroughly with soap and water. If liquid benzyl chloride gets into the eyes, they shall be irrigated immediately with copious quantities of running water.

(7) Medical attention shall be provided promptly for any affected worker. Such exposures shall be reported to the immediate supervisor by the affected worker or by a fellow employee.

(b) Control of Airborne Benzyl Chloride

(1) Appropriate engineering controls designed to limit exposure to benzyl chloride to that prescribed in Section 1(a) shall be used. The use of completely enclosed processes is the recommended method of control for benzyl chloride. Local exhaust ventilation may also be effective, used alone or in combination with process enclosure. When a local exhaust ventilation system is used, it shall be designed to prevent the accumulation or recirculation of contaminated air in the occupational environment, to maintain benzyl chloride concentrations below the recommended limit, and to remove benzyl chloride from the breathing zones of employees. Exhaust systems discharging into outside air must conform with applicable local, state, and Federal air pollution regulations. Ventilation systems shall be subjected to regular preventive maintenance and cleaning to ensure effectiveness, which shall be verified by periodic airflow measurements at least every 3 months. Measurements of system efficiency shall also be made immediately by personnel properly attired in specified protective equipment when any change in production, process, or control might result in increased concentrations of airborne benzyl

chloride. Tempered makeup air shall be provided to work areas in which exhaust ventilation is operating.

(2) Forced-draft ventilation systems shall be equipped with remote manual controls and shall be designed to turn off automatically in the event of a fire in the work area.

(c) Handling of Benzyl Chloride and General Work Practices

(1) Employers shall ensure that safety showers, eyewash fountains, and other emergency equipment are in proper working order through regularly scheduled inspections performed by qualified maintenance personnel.

(2) Personnel attired in appropriate protective clothing and wearing protective equipment shall perform frequent inspections of operating systems to detect any leaks of benzyl chloride. All equipment including valves, fittings, and connections shall be checked for tightness and good working order. All newly made connections shall be checked for leaks immediately after benzyl chloride has been introduced into the system.

(3) Leaks shall be corrected as soon as possible after their detection.

(4) When benzyl chloride containers are being moved or when they are not in use and are disconnected, valve protection covers shall be in place. Containers shall be moved only with the proper equipment and shall be secured to prevent dropping or loss of control while being moved.

(5) Process valves and pumps shall be readily accessible and shall not be located in pits and congested areas.

(6) Containers and systems shall be handled and opened carefully. Approved protective clothing and devices as specified in Section 4 shall be worn while opening, connecting, and disconnecting benzyl chloride containers and systems. Adequate ventilation shall be available to prevent exposure to benzyl chloride when opening containers and systems.

(d) Work Areas

(1) Benzyl Chloride Work Areas

Exits shall be plainly marked and shall open outwardly. Emergency exit doors shall be conveniently located and shall open into areas from which escape is practical.

(2) Confined or Enclosed Spaces

Entry into confined spaces, such as tanks, pits, process vessels, tank cars, sewers, or tunnels, where there may be limited egress, shall be controlled by a permit system. Permits shall be signed by an authorized employer representative certifying that preventive and protective measures have been followed.

Confined spaces that have contained benzyl chloride shall be thoroughly ventilated to ensure an adequate supply of oxygen, tested for benzyl chloride and other contaminants, and inspected for compliance with these requirements before each entry. Adequate ventilation shall be maintained while an employee or other individual is in the space. Leakage of benzyl chloride or other contaminants into the confined space while work is in progress shall be prevented by disconnecting and blanking the supply lines for benzyl chloride and other materials. Individuals entering confined spaces shall be furnished appropriate personal protective clothing and devices and protected by a lifeline harness tended by another employee outside the space who also shall be equipped with personal protective clothing and devices approved for entry. Communication (visual, voice, signal line, telephone, radio, or other suitable means) shall be maintained by the standby person with the employee inside the confined or enclosed space.

(e) Storage

(1) Storage facilities shall be designed to contain spills completely within a surrounding dike and to prevent contamination of workroom air.

(2) Storage of benzyl chloride in contact with reactive metals, such as iron, copper, or aluminum, or in the vicinity of combustibles shall be prohibited.

(3) Benzyl chloride shall be stored in tightly closed containers in a well-ventilated area away from excessive heat and sunlight.

(4) Storage containers shall be periodically inspected for leakage.

(5) Ventilation control switches and emergency respiratory equipment shall be located outside storage areas in readily accessible locations.

(f) Spills, Leaks, and Waste Disposal

(1) If benzyl chloride leaks or spills, the following steps shall be taken:

(A) Evacuate all nonessential personnel from the area.

(B) Adequately ventilate the area of the spill or leak to prevent accumulation of the vapor.

(C) Collect spilled material for reclamation or absorb in vermiculite, dry sand, earth, or similar nonreactive material.

(2) Personnel entering the spill or leak area shall be furnished with appropriate personal protective equipment. All other personnel shall be excluded from the area.

(3) All wastes and residues containing benzyl chloride shall be collected in benzyl chloride-resistant containers and incinerated or buried in such a manner that no benzyl chloride or other toxic products are released to the environment. Prior to disposal, liquid benzyl chloride wastes may be hydrolyzed with alkalies such as lime, soda ash, or sodium bicarbonate to prevent adverse effects on receiving waters or treatment plants.

Section 7 - Sanitation Practices

(a) Plant sanitation shall meet the requirements of applicable portions of 29 CFR 1910.141.

(b) Appropriate locker rooms shall be available for changing into required protective clothing in accordance with 29 CFR 1910.141(e). Clothing contaminated with liquid benzyl chloride shall be immediately removed and placed in a sealed container for later disposal or decontamination. Employers shall require personnel who work with benzyl chloride to shower before leaving the workplace at the end of a workshift.

(c) Employers shall ensure that employees who handle benzyl chloride wash their hands thoroughly with soap and water before eating, smoking, or using toilet facilities.

(d) The storage, dispensing, preparation, and consumption of food, beverages, or tobacco shall be prohibited in benzyl chloride work areas.

(e) The employer shall ensure that plant personnel who launder and clean clothing or equipment contaminated with benzyl chloride are provided adequate personal protective equipment to prevent exposure and shall ensure that these employees are aware of the potential hazards of exposure to benzyl chloride. If an outside laundry facility is used, the launderers shall be advised of the hazards and proper procedures for handling contaminated work clothing. If contaminated clothing is to be transported to a laundry outside of the plant, it shall be placed in sealed containers.

Section 8 - Monitoring and Recordkeeping Requirements

(a) Employers shall determine by industrial hygiene survey whether exposure to airborne benzyl chloride is in excess of the recommended occupational exposure limit. Records of these surveys shall be kept, and if an employer concludes that air levels are at or below the recommended ceiling limit, the records must show the basis for this conclusion. Such surveys shall be repeated at least once every 12 months and within 30 days of any process change likely to result in an increase in the concentration of airborne benzyl chloride. When an industrial hygiene survey demonstrates that the concentration of benzyl chloride exceeds the recommended ceiling limit, the following requirements shall apply:

(b) Personal Monitoring

(1) A program of personal monitoring shall be instituted to identify and measure, or to permit calculation of, the exposure of each employee occupationally exposed to benzyl chloride. Source and area monitoring may be used to supplement personal monitoring.

(2) In all personal monitoring, samples representative of the exposure to benzyl chloride in the breathing zone of the employee shall be collected. Procedures for sampling and analysis of benzyl chloride shall be in accordance with Section 1(b).

(3) For each ceiling concentration determination, a sufficient number of samples shall be taken to characterize employee exposures during each workshift. Variations in work and production schedules, as well as employee locations and job functions, shall be considered in decisions on sampling locations, times, and frequencies.

(4) Each operation shall be sampled at least once every 3 months or as otherwise indicated by a professional industrial hygienist. If an employee is found to be exposed at a level in excess of the ceiling limit, the exposure of that employee shall be measured at least once every week, control measures shall be initiated, and the employee shall be notified of the exposure and of the control measures being implemented. Such monitoring shall continue until two consecutive determinations, at least 1 week apart, indicate that employee exposure no longer exceeds the permissible exposure limit. Quarterly monitoring shall then be resumed.

(c) Recordkeeping

Records of environmental monitoring shall be kept for at least 30 years. These records shall include the dates and times of measurements; duties and location of the employees within the worksite; sampling and analytical methods used; number, duration, and results of the samples taken; ceiling concentrations estimated from these samples; type of

personal protective equipment used, if any; and employees' names. These records shall be made available to designated representatives of the Secretary of Labor, of the Secretary of Health, Education, and Welfare, of the employer, and of the employee or former employee.

# II. INTRODUCTION

This report presents the criteria and the recommended standard that were prepared to meet the need for preventing disease or injury arising from occupational exposure to benzyl chloride. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "develop criteria dealing with toxic materials and harmful physical agents and substances which will describe...exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria on which standards can be established to protect the health and provide for the safety of employees exposed to hazardous chemical and physical agents. The criteria and recommended standards should enable management and labor to develop better engineering controls resulting in more healthful work environments, and simply complying with the recommended standards should not be the final goal.

The criteria and recommended standard for benzyl chloride are part of a continuing series of documents published by NIOSH. The proposed standard applies to the manufacturing, processing, storage, and use of benzyl chloride or to other sources of exposure. The standard was not designed for the population-at-large, and any extension beyond the occupational environment is not warranted. It is intended to: (1) protect against the development of short- and long-term adverse systemic effects; (2) protect against local effects on the skin, eyes, and mucous membranes; (3) be measurable by techniques that are valid, reproducible, and available to industry and government agencies; and (4) be attainable with existing technology.

The development of these criteria for the recommended standard has demonstrated a need for further research in the following areas: (1) epidemiologic studies of the long-term health effects of exposure to benzyl chloride at concentrations bracketing the environmental limit; (2) animal studies designed to determine the cumulative effects from dermal contact with or inhalation of benzyl chloride; and (3) well-designed animal studies to investigate any carcinogenic, mutagenic, teratogenic, or reproductive effects produced by inhalation of, or dermal contact with, benzyl chloride.

## III. BIOLOGIC EFFECTS OF EXPOSURE

### Extent of Exposure

Benzyl chloride ($C_6H_5CH_2Cl$), molecular weight 126.58, is a colorless to light-yellow liquid with a pungent odor [1,2]. It is a strong lacrimator and has an irritating effect on mucous membranes. Benzyl chloride is lipid soluble [3] and is miscible in all proportions with alcohol, chloroform, and ether [4]. Benzyl chloride is considered a moderately volatile liquid, with vapor pressures of 1 mmHg at 22 C, 10 mmHg at 60.8 C, and 100 mmHg at 114.2 C [5]. Some of the important physical and chemical properties of benzyl chloride are listed in Table XI-1.

Benzyl chloride is a commercially important alkylating agent that reacts readily with both organic and inorganic nucleophilic agents and so may also be expected to react with such nucleophiles as amines, carbohydrates, lipids, proteins, ribonucleic acids, and deoxyribonucleic acids in biologic systems. Benzyl chloride reacts rapidly with sulfhydryl groups [6] and binds to the epsilon-amino group of lysine in collagen [7]. Benzyl chloride decomposes relatively slowly in the presence of water. The half-life for the hydrolysis of benzyl chloride, at pH 7 and 25 C, is 15 hours [8]. At 60 C, the rate of hydrolysis is 45 times as fast as at 25 C [9].

In the United States, benzyl chloride is commercially prepared primarily by the continuous photochlorination of toluene [10]. Excess toluene is distilled off and returned to the reactor. Hydrogen chloride gas formed in the reaction is vented to another location where it is absorbed by water to produce a 30% solution that can be sold as muriatic acid. The composition of the crude product is 90-95% benzyl chloride and 5-10% benzal chloride (benzylidene chloride, $C_6H_5CHCl_2$) or benzotrichloride ($C_6H_5CCl_3$) [11]. Further distillation results in a product of greater than 99% purity [12].

Anhydrous benzyl chloride is available in both technical and refined grades [13]. Benzyl chloride undergoes Friedel-Crafts condensation reactions in the presence of such metals as iron, copper, zinc, aluminum, magnesium, and tin. The presence of moisture and/or heat favors such reactions in which the hydrogen chloride released may result in the rapid buildup of pressure in closed containers [1,5,14,15]. A stabilizer such as propylene oxide, triethylamine, or sodium carbonate often is added to inhibit these condensation and decomposition reactions by neutralizing acidity and scavenging free radicals [1,14]. Benzyl chloride is shipped in glass carboys, phenolic-lined steel or returnable nickel drums, tank cars, and tank trucks. It has an effective storage life of 2-3 months at normal temperatures.

Currently, there are four major manufacturers of benzyl chloride in the United States [16]. Domestic production increased at the relatively steady rate of 5.6% a year from 1964 to 1974 [17]. Some of the demand, especially in the textile industry, appears to be leveling so that a growth rate of 4% a year has been predicted through 1979 [17]. Total US production increased from 10.4 million pounds in 1950 to an estimated 90 million pounds in 1976 [16].

In 1972, the last year for which such figures are available from the US Tariff Commission [16], approximately 77% (as calculated by the sales figures given) of the total benzyl chloride produced was used captively by its manufacturers mainly for the preparation of butyl benzyl phthalate and benzyl alcohol [16].

At present, an estimated 60-70% of the benzyl chloride manufactured in the United States is devoted to the production of n-butyl benzyl phthalate, a plasticizer for the flexible vinyl polymers used in coatings and floor coverings [16,17]. Benzyl alcohol, the manufacture of which accounts for 10-15% of the benzyl chloride output, is used as an adjunct in the dispersion, uptake, and rate of fixation of dyes in the textile industry and to make specialized solvents. Another 10-12% of the benzyl chloride output is used to form a variety of quaternary ammonium compounds that are used as germicides, fungicides, and sanitizers and in products such as hair conditioners, wetting agents, dispersing agents, and emulsion paint preservatives. The remaining 5-10% of benzyl chloride production is used in the synthesis of such materials as benzyl acetate, benzyl cyanide, benzyl salicylate, benzyl butyrate, and benzylamines, many of which are prepared on batch or campaign bases [16]. These products are used in the pharmaceutical, perfume, flavors, and dye industries. Benzyl chloride is reported to be effective as an extreme-pressure lubricant [18,19], the lubricating property of which is attributed to a chloride film that forms on iron surfaces [18]. In other applications, benzyl chloride can undergo condensation reactions forming low molecular weight polybenzyl resins that are temperature- and pressure-stable and noncorrosive [20] and have been proposed for use as hydraulic fluids, heat transfer fluids, and heat-stable fuel. Imports of benzyl chloride derivatives in 1974 were reported to have amounted to about 1.48 million pounds, approximately 1% of the domestic market [16].

NIOSH estimates that 3,000 workers in the United States are potentially exposed to benzyl chloride. Occupations involving potential exposure to benzyl chloride are listed in Table XII-2.

## Historical Reports

Wolf [21], in 1912, described his personal experience when he was exposed to benzyl chloride vapor while conducting animal experiments. He

experienced a severe burning sensation in his eyes and copious tearing when he opened the exposure chamber at the beginning and end of the experiments. These effects, present even at the nominal concentration of 160 mg/cu m, were accompanied by conjunctivitis at higher concentrations. Wolf also noted some nasal irritation. Schutte [22], during similar experimental procedures, experienced a burning sensation in his eyes on the 1st day of exposure; an inflammation of the upper respiratory mucous membranes developed, accompanied by free discharge that persisted for the remaining several weeks of the tests.

In 1919, Hill [23] of Birmingham, England, patented the use of the noxious properties of benzyl chloride to disable enemy troops. He proposed mixing 35-60 grains (2.3-3.9 g) of benzyl chloride with 1 ounce (28 g) of light magnesium carbonate to aid in its dispersion and volatilization. When packed into shells, grenades, and bombs, to be shot among the enemy, the powder, with its coating of benzyl chloride, would allegedly remain suspended in the air and expose the troops to the noxious effects of benzyl chloride. There are no reports of the actual use of this system. According to Meyer's 1926 report [24], benzyl chloride and the other benzyl halides did not play significant roles as noxious agents during World War I. The starting material, toluene, had become expensive and had a higher priority in the manufacture of trinitrotoluene. Also, because atomized benzyl chloride lacked long-lasting effects, its use as a war gas was superseded by a more potent irritant, bromobenzyl cyanide [24]. Meyer stated that benzyl chloride vapor at 85 mg/cu m was intolerable to humans. No supporting information was given. Flury and Zernick [25], referring to Meyer's work, concluded that 16 ppm (85 mg/cu m) was intolerable to man in 1 minute, although Meyer had not specified a time.

In 1929, Lallemand [26] rated benzyl chloride as rapidly toxic to the developing chicken embryo. A toxic time was defined as the duration of exposure to a saturated atmosphere of a gaseous or volatile chemical at 18 C that would arrest the development of a chicken embryo, but not of the blastoderm, when it was returned to normal incubation conditions for 48 hours. Unexposed control embryos did not develop at 18 C, but both embryonic and blastodermal development resumed after a 48-hour normal incubation. The toxic time for benzyl chloride was 5 hours.

## Effects on Humans

Watrous [27], in 1947, reported some of his observations of toxic effects related to the use of certain halides as intermediates in the pharmaceutical industry. He observed some instances of conjunctivitis and upper respiratory tract irritation in a small group of workers that he described as intermittently exposed to benzyl chloride vapor (up to 500 ppm, 2,590 mg/cu m), and he ascribed a vesicant action to liquid benzyl chloride without, however, citing any examples. The duration of exposure

was not indicated. Smyth [28] in 1956, commented that "This (benzyl chloride) is a potent lacrimator irritating to eye, nose, and throat and capable of causing lung edema.... It may be inferred that the liquid causes severe corneal injury."

In the 1971 edition of the Encyclopedia of Occupational Health and Safety published by the International Labour Office (ILO), Mikhailova [29] reported that production workers exposed to benzyl chloride at 10 mg/cu m and above complained of weakness, rapid fatigue, persistent headaches, increased irritability, a hot feeling, loss of sleep and appetite, and, in some, itching skin. Medical examination of workers revealed instances of weakness, sweating, localized tremors, poor proprioception, and dermatographism. Findings of abnormally high blood bilirubin, abnormally low leukocyte counts, and nonspecific abnormalities in the serum protein levels (positive Takata-Ara and Weltmann tests) suggested to the author a disturbance of liver function. Because the number of workers, working conditions, actual range of benzyl chloride exposures, and other exposure details are unknown, the reports of signs and symptoms attributed to exposures to benzyl chloride at concentrations greater than 10 mg/cu m are questionable.

In a 1930 technical report prepared for the US Bureau of Mines, Katz and Talbert [30] listed the odor and irritation thresholds of some volatile chemicals, including benzyl chloride. In each test series, five or six persons were exposed to the vapor of commercially prepared benzyl chloride, having a boiling point of 174-180 C at 745 mmHg. The vapor concentration in the primary airstream was calculated (considering the vapor as a perfect gas) as the weight loss of the vaporizer divided by the product of air flowrate and time.

Volunteers remained in an outer ventilated room except for the few seconds of testing [30]. For the odor and nasal irritation tests, each subject lifted the cover of a small, strongly ventilated hood, placed his nose well into the nosepiece, and took one breath. He then recorded the intensities of odor and pain perceived according to separate rating scales. To test for ocular irritability, each subject held one eye open to the airstream at the nosepiece for 10 seconds. Eye irritation was recorded as pain perceived, according to the same rating scale used for nasal irritation.

Participants described the odor of benzyl chloride as "aromatic, benzene-like" [30]. They rated benzyl chloride odor as "just perceptible" at 0.21 mg/cu m, "faint" at 1.7 mg/cu m, "easily noticeable" at 13 mg/cu m, and "strong" at 110 mg/cu m. Eye irritation was rated as "just perceptible" at 41 mg/cu m, "very unpleasant" at 88 mg/cu m, "painfully strong" at 190 mg/cu m, and "intolerable" at 410 mg/cu m. Nasal irritation was rated as "just perceptible" at 180 mg/cu m.

Mikhailova [29] further stated that benzyl chloride at 160 mg/cu m was unbearably irritating, that 50-100 mg/cu m caused immediate tearing and eyelid twitching, and that 5 minutes of exposure at 6-8 mg/cu m caused a slight conjunctivitis. She stated that benzyl chloride production workers showed an increased tendency toward respiratory illnesses (similar to colds and allergic rhinitis) and dermatitis. This report did not include important information such as sampling and analytical methods, number and percentage of the workers affected, possible exposures to other chemicals, or time before onset of effects. In spite of the absence of these details, which would allow validation of the information contained in the abstract, and considering the variability involved in the subjective evaluation of pain by individuals, it appears that the ocular effects described by Mikhailova at 6-160 mg/cu m substantially agree with those of the laboratory study by Katz and Talbert [30].

Leonardos et al [31], in 1969, reported the odor recognition thresholds of benzyl chloride and 52 other chemicals. The chemicals were presented to a panel of four analysts who had been trained to recognize odor quality and character. The odor threshold was defined as the lowest concentration at which all four panelists could positively identify an odor that, in turn, could be consistently recognized at higher concentrations.

The odor threshold for benzyl chloride was determined to be 0.047 ppm (0.24 mg/cu m), or about 1/100 that of benzene and 1/50 that of toluene [31]. The authors suggested that the experimentally determined odor recognition value for benzyl chloride was probably lower than it would have been under environmental background conditions.

Many investigations concerning the metabolic fate of benzyl chloride have been conducted in animals (see Animal Toxicity). Glutathione-S-transferases, which catalyze the conjugation of benzyl chloride with glutathione and which have been reported in several animal species, have also been isolated from human liver and show activity with benzyl chloride substrate [32] (See Table III-1).

## Epidemiologic Studies

No epidemiologic reports on benzyl chloride were located in the literature.

## Animal Toxicity

(a) General

Back et al [33], in 1972, reported the results of a study they performed for the US Department of Transportation. Benzyl chloride was classified as a toxic agent for transportation purposes based on rat and mouse oral and inhalation toxicity data. The classification was said to be

TABLE III-1

DISTRIBUTION OF GLUTATHIONE-S-TRANSFERASES IN DIALYZED LIVER SUPERNATANTS FROM DIFFERENT SPECIES

| Species | No. and Sex | Aralkyltransferase Activity (Benzyl Chloride Substrate) Relative | Measured* |
|---|---|---|---|
| Rat** | 30 M,F | 1.00 | 2.3 |
| Dog | 1 F | 0.91 | 2.1 |
| | 1 M | 0.48 | 1.1 |
| Guinea pig | 3 M | 3.26 | 7.2 |
| Mouse** | 20 M | 0.83 | 1.9 |
| Rabbit | 1 M | 0.48 | 1.1 |
| Ferret | 2 M | 0.13 | 0.3 |
| Pigeon** | 6 M | 1.43 | 3.3 |
| Hamster** | 5 M | 0.83 | 1.9 |
| Human (post mortem) | 1 F | 0.22 | 0.5 |
| Human (fetus) | 2 M | 0.30 | 0.7 |

*Micromoles thiol lost/min/g tissue
**Tissues pooled

Adapted from reference 32

applicable to any substance that had, after a single exposure, a 1-hour $LC_{50}$ of 200-20,000 ppm (1,036-103,600 mg/cu m for benzyl chloride) or a 14-day oral $LD_{50}$ of 50-5,000 mg/kg. The authors cited the oral $LD_{50}$ of benzyl chloride for rats as 1,231 (95% confidence limits 1,145-1,656) mg/kg and for mice, 1,624 (1,153-2,185) mg/kg. They also reported that rats and mice survived a 1-hour exposure to benzyl chloride at 2,000 mg/cu m. No information on experimental design was given.

Mikhailova [34], in 1964, reported the acute lethal effects of benzyl chloride and of benzal chloride and benzotrichloride, which are sometimes present as contaminants of benzyl chloride. The compounds were tested in a total of 140 adult male rats and 82 white mice of unspecified sex, age, weight, and strain. An unspecified number of rats and mice were exposed for 2 hours in a 100-liter static chamber to determine the $LC_{50}$ of each of these compounds, the vapor concentrations of which were measured spectrophotometrically. The rats were observed for 1 month and the mice for 2 weeks after exposure.

In mice, the $LC_{50}$ values were 390 mg/cu m for benzyl chloride, 210 mg/cu m for benzal chloride, and 60 mg/cu m for benzotrichloride [34]. In rats the $LC_{50}$ values were 740 mg/cu m for benzyl chloride, 400 mg/cu m for benzal chloride, and 150 mg/cu m for benzotrichloride. The author observed that all three compounds when inhaled at concentrations greater than 100 mg/cu m produced signs of excitement, ocular and respiratory mucosal irritation, and slowed respiration in both species. She also noted a marked hyperemia of the ears, paws, and tails of animals throughout the experiment. Only at concentrations of about 1,000 mg/cu m were there signs of such nervous system effects as unresponsiveness and slowed respiration (in both species), motor automatism (in mice), and peripheral muscle twitching (in rats).

Examination of animals that died during the study revealed respiratory tract inflammation (fibrin films, desquamation of epithelium, edema, and submucosal hemorrhages) [34]. A superimposed secondary infection was generally noted if the animals died 12-14 hours after exposure. Evidence of plethora, stasis, and blood effusions was found in all organs examined. Changes, described as both albuminoid and fatty degeneration, were found in the hepatic cells. Albuminoid degeneration of the convoluted tubular epithelium, sometimes leading to necrosis, also was reported. Unspecified degenerative changes were noted in the myocardium and brain.

Another experiment was conducted to observe recovery from the effects of single 2-hour exposures to each compound at 100 mg/cu m [34]. Groups of 10 male white rats of approximately equal weight and a 10-rat control group, which was placed in a control chamber for 2 hours, were monitored for 1 month following exposure. Body weights, general condition, thresholds of neuromuscular excitability, renal function (18-hour water loading and 24-hour protein measurements), and blood counts were determined at regular, but unspecified, intervals.

Loss of body weight was commonly noted in rats that underwent single 2-hour exposures to any of the three compounds at 100 mg/cu m [34]. Animals exposed to benzyl chloride showed a mean loss of 15 ±3 g, whereas controls had gained 11 ±2 g by the 5th day after exposure. The weights of rats exposed to benzyl chloride had returned to their initial values at 14 days and had increased above this weight by 29 3.7 g at the end of the 30-day observation period. The mean total weight gain in control rats during this time was 41 ±3.3 g. Weight losses were greater following benzal chloride exposure (18 ±3 g) and most severe after benzotrichloride (36 ±4 g) at the 5th day after exposure. No remarkable changes in renal function were found following exposure to benzyl chloride or benzal chloride, but a decrease in urine produced after water-loading was found 3 weeks after exposure to benzotrichloride. Peripheral blood cell counts and hemoglobin levels in benzyl chloride- and benzal chloride-exposed animals were essentially the same as control values, but leukocyte and erythrocyte counts were slightly lower in rats 1 month after exposure to benzotrichloride.

Mikhailova [34] concluded that the toxicities of all the three compounds were similar qualitatively but quantitatively became more severe with increasing replacement of hydrogen by chlorine on the side chain. However, since benzotrichloride, the most toxic of these three substances, was the least volatile and since the volatility and toxicity of benzal chloride were intermediate between those of benzotrichloride and benzyl chloride, the author suggested that there was a differing probability of actual inhalation absorption for each of these substances and that their net effects singly might be similar under identical environmental conditions.

The $LC_{50}$ data obtained by Mikhailova [34] do not agree with those of Back et al [33]. Mikhailova reported 50% lethality in rats after a 2-hour exposure to benzyl chloride at 740 mg/cu m, whereas Back et al stated that all rats survived a 1-hour exposure to benzyl chloride at 2,000 mg/cu m. Since important experimental details were not provided in either report, the differences in results cannot be explained.

In 1912, Wolf [21] reported the results of single and repeated exposures of nine cats and one rabbit to benzyl chloride vapor. The ages and sexes of the animals were not specified. A stream of air was forced through sulfuric acid to remove moisture and then directed through a bottle of benzyl chloride and into the glass chamber. Another stream of fresh air was used as a diluent, and its flowrate was measured with a water wheel with a gas gauge. The loss of weight of the benzyl chloride in the bottle divided by the ventilation rate of the chamber yielded the nominal concentration of benzyl chloride in mg/liter of air.

Seven cats were exposed continuously for 8 hours at 160-3,330 mg/ cu m [21]. One rabbit also was exposed at 480 mg/cu m for 8 hours. One cat

exposed for 8 hours at 160 mg/cu m was reexposed 6 days later for 3 hours to benzyl chloride at 2,480 mg/cu m. Two additional cats were exposed for 7.0 and 7.5 hours at respective concentrations of 7,000 and 17,700 mg/cu m. All animals were observed during and after exposure until either recovery or death occurred. All animals that died were examined grossly.

Of the seven cats and one rabbit exposed for 8 hours at 160-3,330 mg/cu m, the one cat exposed at 160 mg/cu m, two cats exposed at 480 mg/cu m, and the one cat exposed at 630 mg/cu m recovered within 12-15 hours after exposure [21] . They showed little residual effect except for moderate conjunctivitis. The rabbit exposed at 480 mg/cu m recovered immediately after exposure. The cat exposed to benzyl chloride at 890 mg/cu m died on the 9th day. The cat that was originally exposed at 160 mg/cu m for 8 hours and reexposed 6 days later at 2,480 mg/cu m for 3 hours recovered after 24 hours. Both cats exposed at 3,330 mg benzyl chloride/cu m of air for 8 hours died within 24 hours. The two cats exposed at the highest concentrations of benzyl chloride, 7,000 and 17,700 mg/cu m of air for 7.0 and 7.5 hours, respectively, died within 0.5 hour after cessation of exposure.

From Wolf's [21] observations, intense local inflammation (and sequelae) of the mucous membranes of the eyes, nose, mouth, and all the tubular air passages to the pulmonary alveoli were the main effects of exposure by inhalation to benzyl chloride vapor in cats and, to a lesser extent, in the rabbit. These effects were observed at all tested concentrations; however, the severity of these reactions varied directly with the concentration and duration of exposure. The immediate results of exposure were eyeblinking, eyelid closing, tearing, salivation, sneezing, and coughing. At 630 mg/cu m, a greatly increased respiratory rate, up to three times the normal rate, was followed by a marked decrease. The respiration then became irregular. At 2,480 mg/cu m and above, the animals progressed to inactivity and marked unresponsiveness, until either fresh air was supplied or death occurred. Autopsies on cats exposed to benzyl chloride at 890 mg/cu m and above revealed markedly increased mucoid, often hemorrhagic secretions throughout the respiratory organs, with patches of edematous or hemorrhagic consolidation of the lungs, and severe pneumonia in a cat that survived for a few days after exposure. One cat had severe conjunctivitis and clouded corneas.

The two cats and one rabbit that had been previously exposed at 480 mg/cu m for 8 hours were reexposed at the same concentration and for the same duration for 5 more consecutive days [21]. The cats showed a mild to moderate conjunctivitis that, after the 1st day, became more marked with subsequent exposures. Both cats gradually developed severe coughs, one by the 2nd and the other by the 4th day, which persisted for an unspecified time beyond the exposure period. Their appetites decreased each day. One of the cats did not recover; however, no autopsy was reported. The rabbit showed signs of mild eye irritation, but not of conjunctivitis, during the

exposure period, and a perceptible reddening of its oral and nasal membranes occurred by the 6th day. Salivation, coughing, sneezing, or tearing were absent, and the rabbit maintained its appetite. These results indicate that the effects of benzyl chloride may become more severe with repeated exposure.

Using the method described by Wolf [21], Schutte [22], in 1915, reported his observations on 12 cats, 5 rabbits, and 1 dog that had been exposed to benzyl chloride at 800-23,600 mg/cu m of air for 0.5-8 hours. Initial weight, but not age or sex of the test animals, was reported. As in the acute study by Wolf [21], all animals were observed until recovery or death occurred. Autopsies were performed on the animals that died.

Two cats and one rabbit exposed at 1,100 mg/cu m for 7.5 hours died within 2 days [22]. However, one cat and one rabbit exposed at 1,500 mg/cu m for 6 hours recovered; the cat that survived developed bronchitis. The rabbit was exposed 4 days later to 9,600 mg/cu m for 2.25 hours. Two cats exposed at 2,000 mg/cu m for 0.5 hour, and one cat and one rabbit exposed at 3,900 mg/cu m of air for 2 hours, recovered rapidly except for slight conjunctivitis in one cat. All cats exposed at 5,300-9,600 mg/cu m for 2-2.5 hours died within 2 days. Two cats exposed at 23,600 mg/cu m for 0.5 hour appeared to have recovered but died within the next 3 weeks. The three rabbits exposed at 6,600-9,600 mg/cu m for 2-2.25 hours died within 10 days. The dog died within 24 hours after an 8-hour exposure to benzyl chloride at 1,900 mg/cu m. The two cats initially exposed to benzyl chloride at 2,000 mg/cu m for 0.5 hour, which, as previously stated, appeared to recover rapidly, were reexposed 5 days later at 800 mg/cu m for 0.5 hour. By the next day, their breathing was audible and labored; both died of pneumonia within 3 weeks. It appears that after initial exposure the animals became less resistant to reexposure.

Schutte's [22] observations agreed with those reported by Wolf [21]. The immediate effects of benzyl chloride were severe irritation of the eyes and, to a lesser degree, the nasal mucosa. After a 0.5-hour exposure at the lower concentrations and sooner at the higher concentrations, benzyl chloride appeared to exert a narcotic effect as indicated by the animals' passive behavior. In one cat exposed at 1,500 mg/cu m and in others exposed at higher levels, the author noted disturbances in equilibrium and occasional tremors. Corneal turbidity was reported in seven animals after inhalation exposure at 1,100-11,500 mg/cu m, but it cleared within 3 days in the cat exposed at 1,500 mg/cu m. Serious but unspecified changes were seen in the respiratory organs of the animals that died.

In a 1936 paper, Landsteiner and Jacobs [35] discussed the induction of sensitization by benzyl chloride in guinea pigs. Benzyl chloride in saline solution at a dose of 0.01 mg/animal was injected intracutaneously twice weekly for 12 weeks into an unstated number of guinea pigs. Two weeks

later, sensitization tests were conducted on these animals. The details of this test were not reported, but the procedure may be inferred from other experiments reported in the same paper [35], ie, a drop of the test solution mixed with olive oil was spread on a shaved flank of each animal. The authors noted positive effects that were not specified; it may also be inferred from related experiments that these effects included erythema and some swelling of the treated site. The authors concluded that benzyl chloride had a sensitizing capacity.

Holmberg and Malmfors [36], using Ehrlich-Landschutz diploid (ELD) ascites tumor cells, examined the cytotoxic effects of benzyl chloride at volumetric concentrations of 50 and 100 ppm in cell suspensions ($1 \times 10^6$ cells/ml) that were incubated for up to 5 hours at 37 $\pm$1 C under constant stirring in sealed 3-ml glass tubes. The increased permeability of ELD ascites tumor cells to Lissamine green induced by organic solvents was considered to be a stage of irreversible cellular damage preceding cell death. Even at 100 ppm benzyl chloride, the proportion of dead ELD cells increased from 5.0% at 0 time to 14.5% after 5 hours of incubation, which the authors concluded was a moderate cytotoxic reaction. However, because these experiments were carried out on ascites tumor cells in vitro, the results are only suggestive of a cytotoxic effect of benzyl chloride in vivo, but may explain some of the tissue changes found in the respiratory system following exposure at high concentrations [21,22,34].

Stekol [37], in 1947, studied the growth patterns in young rats fed a diet that included various amounts of sulfur-containing amino acids and benzyl chloride. For these experiments, a basal diet was formulated that the author considered to be nutritionally complete, but with a low sulfur content. Commercially pure benzyl chloride, 0.5% by weight, was added to the basal diet for 7-10 days. This was alternated with periods of 10-21 days during which the basal diet alone or with benzyl chloride with and without supplements of l-cystine, d-cystine, dl-methionine, dl-homocystine, or taurine was given.

All animals lost weight while on the benzyl chloride diet [37]. The weight loss was alleviated, and normal growth rates were resumed when the diet was supplemented with l-cystine, dl-methionine, or dl-homocystine. Taurine and d-cystine, which are not considered cysteine sources, did not stop this weight loss. The author stated that although there was a "significant reduction of food consumption" in animals on the benzyl chloride diet, this alone could not account for the inhibition of growth that was observed. He suggested that this was due, at least in part, to interference by benzyl chloride with utilization of the sulfur-containing amino acids needed for growth. Because benzyl chloride was added directly to the diet, its conjugation with sulfur-containing amino acids may have occurred prior to its ingestion. Stekol mentioned, but did not report data on, controls with the same lowered food intake.

(b) Metabolism

One of the major excretion products following ingestion of benzyl chloride is a cysteine conjugate, benzylmercapturic acid [38-42]. Most studies of the metabolism of benzyl chloride have been concerned with aspects of the detection and the mechanism of formation of this conjugate in rats, rabbits, mice, dogs, and quinea pigs. A proposed pathway for the formation of benzylmercapturic acid from benzyl chloride is presented in Figure III-1.

Stekol [39], in 1938, described the recovery of N-acetyl-S-benzyl cysteine (benzylmercapturic acid) from dog urine following the feeding of benzyl chloride and S-benzylcysteine. In a later (1939) study [38], he also isolated benzylmercapturic acid from the urine of rats and rabbits administered benzyl chloride subcutaneously (sc) in an unspecified carrier.

Witter [40] found no increase in sulfur, and thus no increase in benzylmercapturic acid, in the urine of rabbits injected sc with 260 mg benzyl chloride suspended in 10 cc of gum tragacanth solution but did report an increase in urinary nitrogen that he considered indicative of tissue damage. However, urinary nitrogen/creatinine ratios remained within the range of control values. Open sores that developed several weeks later at injection sites suggested to Witter that benzyl chloride in gum tragacanth solution was poorly absorbed and had irritating properties when left in contact with tissue. No such irritation was reported following injection of gum tragacanth solution alone.

In a 1958 study, Bray et al [43] examined the metabolic products detectable in rabbit urine following oral administration of 200 mg benzyl chloride/kg body weight. Urine was collected for approximately 24 hours and analyzed. The ether-soluble acid fraction of the rabbit urine accounted for 86.4% of the dose administered: 49% as benzylmercapturic acid, 20% as a glycine conjugate, 0.4% as glucosiduronic acid, and 17% possibly excreted as unconjugated benzoic acid. No glucuronic acid and no ethereal sulfate were detected. Maitrya and Vyas [44], as reported in 1970, gave benzyl chloride to six rats in oral doses of 44 mg/kg body weight daily for 7 days. Urine samples were collected and analyzed for hippuric acid only, by Quick's method [45]. Of the total amount of benzyl chloride administered, 30% was excreted as hippuric acid.

Knight and Young [42], using radiochromatographic and isotope dilution methods, concluded that benzyl chloride, unlike related compounds including chlorinated benzenes, is converted directly into benzylmercapturic acid without the formation of acid-labile precursors.

Barnes et al [41] measured the rate and amount of benzylmercapturic acid formation in the urine of fasted female rats after oral administration of an aqueous suspension of 158 micromoles benzyl chloride/100 g body weight (200 mg/kg). Urine was collected from four rats until no more

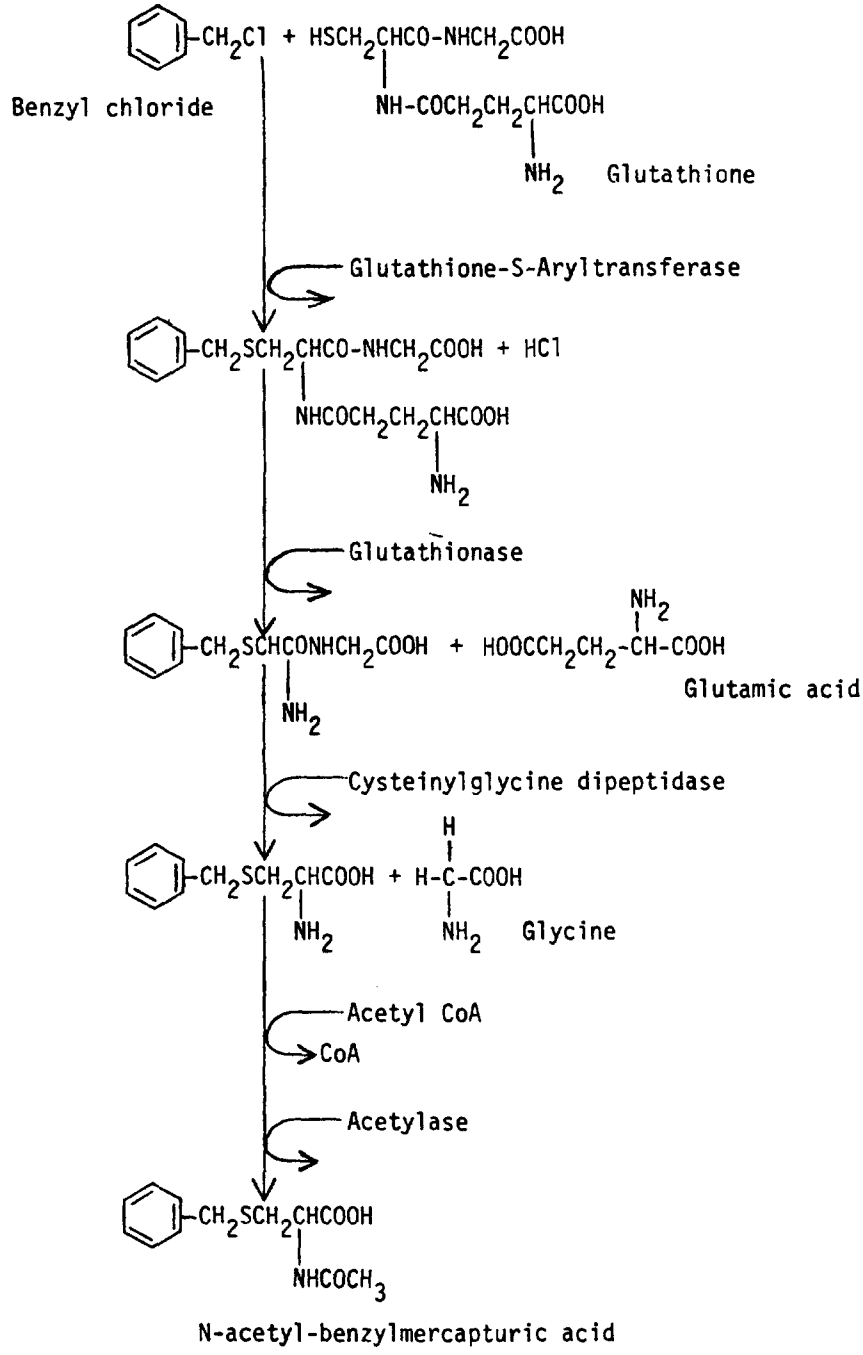


FIGURE III-1

A PROPOSED PATHWAY FOR BENZYLMERCAPTURIC ACID FORMATION FROM BENZYL CHLORIDE IN RATS*

*Adapted from reference 64

mercapturic acid could be detected (usually 24 hours). To measure the rate of mercapturic acid formation, the authors again administered six fasted rats with 158 micromoles benzyl chloride/100 g body weight. Two hours after benzyl chloride administration, the urine in the bladder of the rats was expelled by gentle pressure and discarded. At this time, and again 3 hours later, 3 ml of water was given by stomach tube. All urine produced between hours 2 and 6 was collected and pooled. Preliminary experiments conducted at 2-hour intervals showed that the rate of mercapturic acid excretion was nearly constant during this period [41].

The mean total benzylmercapturic acid excretion in the rat corresponded to 27% (range 20-32%) of the benzyl chloride administered [41]. Bray et al observed these values to be 49% in the rabbit [43] and 4% in the guinea pig [46] after similar doses of benzyl chloride. The mean maximal excretion rate during the 2-6 hour period was calculated to be 5.8 micromoles/100 g/hour (3.5-7.8), ie, 14.7 mg/kg body weight/hour. The excretion rate was almost constant during that period but began to decline slightly by the 6th hour.

Stekol [39] noted that the thiol group of benzylmercapturic acid was attached to the carbon of the side chain instead of directly to a ring carbon, as in the conjugation of other aromatics such as halogenated benzenes, anthracene, and naphthalene [47]. He suggested that the affinity of benzyl chloride for thiol groups was a common factor in the mechanism of its detoxification and of its sensitizing properties.

Stekol's [39] observations raised a question regarding the source of the thiol group in benzylmercapturic acid. In contrast to Stekol's explanation that benzyl chloride conjugated with tissue protein, Barnes et al [41] postulated that the conjugation might have been with the tripeptide, glutathione. They calculated glutathione turnover rates from maximum excretion rates of mercapturic acid and from the levels of glutathione in the rat liver before and after administration of benzyl chloride.

Glutathione levels in the liver were significantly lower in the 5-11 rats administered benzyl chloride compared with the 4-12 water-fed controls [41]. The mean values for reduced glutathione (GSH) in benzyl chloride-dosed rats were 38, 16, 20, 27, and 70 mg/100 g of liver at 0.5, 2, 4, 6, and 10 hours, respectively. The corresponding values for water-fed controls were 120, 163, 140, and 133 mg/100 g of liver (no 10-hour sample). The mean values for oxidized glutathione (GSSG) in benzyl chloride-dosed rats at 0.5, 2.0, and 4.0 hours, respectively, were 21, 4, and 15 mg/100 g of liver in the benzyl chloride-fed rats and 53, 14, and 35 mg/100 g of liver in the control rats.

The turnover rate of glutathione in the liver was calculated by an adaptation of the method of Simkin and White [48], based on the depletion

of free glycine in the liver and the excretion of benzoic acid, the precursor of hippuric acid [41]. Turnover rates were 49 mg/100 g of liver/hour for GSH, and 50 mg/100 g of liver/hour for GSH + GSSG. With the formula $t^{0.5} = 0.7$ g/v where g is the normal glutathione level of the liver (176 mg/100 g of liver) and v is the turnover rate, half-lives of 2.1-4 hours (mean 3.1) were calculated; this finding agrees well with those of other investigators [49,50].

The marked drop in the liver glutathione levels of rats administered benzyl chloride was roughly proportional to the amount of mercapturic acid formed [41]. Barnes and coworkers concluded that the rate of glutathione turnover was adequate to account for the amount of mercapturic acid formed.

The data [41] implicating liver glutathione as the source of thiol groups for mercapturic acid formation are supported by a study reported in 1967 by Suga et al [51] who determined the distribution of the enzyme that conjugates glutathione with benzyl chloride in various organs of the rat. The crude enzyme remained in the 105,000 x g liver supernatant fraction, ie, it was not microsomally bound. Activity of the enzyme was measured by its ability to accelerate the conjugation of glutathione with a benzyl chloride substrate. The reaction rate for liver enzyme with benzyl chloride was constant for 30 minutes. Rat liver had the highest glutathione-conjugating activity; the kidney had 73% and the spleen 13%, whereas the brain, intestine, lung, and heart each had 4% or less, compared with the liver.

The previous conclusion by Barnes et al [41] that glutathione turnover was sufficient to account for the thiol source for mercapturic acid synthesis was strengthened by the report of Bray et al [52] that assessed the relative importance of glutathione and protein thiol groups as conjugating agents for benzyl chloride in liver homogenates from adult female rats. The authors found a rapid drop in glutathione levels after the addition of 53 millimoles of benzyl chloride/100 g of liver. Glutathione levels (in millimole/100 g of liver) decreased in the following manner: 0.64 at 0.5 minutes, 0.21 at 2.0 minutes, 0.09 at 4.0 minutes, 0.03 at 6.0 minutes, and 0.02 at 8.0 minutes. In the same preparations, nonglutathione thiol levels averaged 1.68 millimoles/100 g of liver for the 8 minutes. Control glutathione levels remained at about 0.88 millimoles per 100 g of liver. The authors concluded that because the initial drop in glutathione was so rapid, benzyl chloride probably conjugated with glutathione rather than with general tissue protein. Beck et al [53], in 1964, also found liver glutathione levels reduced (by 50% in 2 hours) after intramuscular administration of benzyl chloride in mice.

(c) Carcinogenic and Mutagenic Effects

The first evidence of tumor production by benzyl chloride was published in a 1968 preliminary report by Preussmann [54]. In 1970, Druckrey et al

[55] published the full-text report of the study in which 12 direct alkylating agents were screened for carcinogenic activity in rats. The authors first conducted an acute toxicity ($LD_{50}$) experiment to determine appropriate dose levels for the chronic study. Benzyl chloride, purified by double distillation and dissolved in peanut oil, was administered sc to 100-day-old rats of 3 BD strains. The $LD_{50}$ was determined to be 1 g/kg, with deaths occurring after 1-4 days. No information was provided on dosage or numbers of animals used in the toxicity tests. The toxic signs observed during the acute toxicity tests were said to have been similar for each of the 12 agents studied, but the results for benzyl chloride were not specifically reported. The initial toxic sign that appeared about 20 minutes after administration was lassitude. Later, in 10-20 hours, signs of lung edema with increasing labored breathing were observed in all animals. A hemorrhagic diarrhea developed. Autopsy confirmed the diagnosis of lung edema with hemorrhages. Liver damage, not further characterized, was found in many of the injected animals.

Two dose levels were then selected for the chronic study with benzyl chloride [55]. In the chronic test, 14 rats were injected sc with benzyl chloride at a dose of 40 mg/kg and 8 other rats were injected with 80 mg/kg once weekly for 51 weeks. According to the authors, these represented total doses of 2.1 and 3.9 g/kg, respectively.

After a mean induction time of 500 days, 3 of the 14 animals that had received the 40 mg/kg dose had injection-site sarcomas; and 6 of the 8 animals given the 80 mg/kg dose had larger sarcomas, most of which had metastasized to the lungs [55]. By microscopic examination of the injection-site tumors, six fibrosarcomas, two spindle cell sarcomas, and one myosarcoma were identified. Benzyl chloride-induced tumors were reported to be transplantable. It was not clear from the authors' description and table of results which types of tumors were associated with the high (80 mg/kg) doses and which with the low (40 mg/kg). It was also impossible to determine which tumors had metastasized and which were transplantable. A moderate local necrosis at the site of injection also was observed. A control group of rats injected with pure peanut oil at and above the volume used as a carrier did not develop local sarcomas.

Poirier et al [56], in 1975, reported the results of a study of the correlation between the chemical reactivity of 17 low molecular weight alkyl halides and their carcinogenic activity as measured by induction of pulmonary tumors in A/Heston strain mice. All compounds, including benzyl chloride, were more than 98% pure. Each group of 20 male and female mice, 6-8 weeks old and weighing 17-19 g, was injected intraperitoneally (ip) 3 times/week for 8 weeks at one of three dose levels of benzyl chloride solubilized in tricaprylin. Mice receiving no injections, and mice given injections of tricaprylin alone, served as negative and vehicle controls, respectively. Mice injected with two dose levels of urethane served as positive controls.

The maximum tolerated dose (MTD), defined as the maximum single dose that at least four of five mice tolerated after receiving six ip injections in 2 weeks, was determined for each chemical [56]. Three experimental groups received the MTD, or a 1:2 or 1:5 dilution of the MTD. The authors stated that because of its toxicity, fewer doses of benzyl chloride were administered than originally planned. Toxic effects were not specified. A total of 15.8 millimoles/kg (2 g/kg) benzyl chloride was given in 8 doses, 11.8 millimoles/kg (1.5 g/kg) in 12 doses, and 4.7 millimoles/kg (0.6 g/kg) in 12 doses.

Twenty-four weeks after the initial injections of benzyl chloride, the surviving mice were killed by cervical dislocation[56]. There were 8/20 survivors at the 2 g/kg, 16/20 at the 1.5 g/kg, and 15/20 at the 0.6 g/kg dose. The lungs were removed and fixed in Tellvesniczky's fluid for 3-4 days. Tumors, which appeared as pearly white nodules on lung surfaces, were counted, and some of these were examined microscopically. The average number of lung tumors/mouse injected with the 2-g/kg dose of benzyl chloride was 0.25 ±0.08. There was an average of 0.50 ±0.13 for the 1.5 g/kg and 0.26 ±0.07 for the 0.6 g/kg dose. The results after benzyl chloride injection were not significantly different, as determined by the standard Student's t-test, from either the untreated (0.21 ±0.03) or the tricaprylin-vehicle-treated (0.24 ±0.05) mice. Urethane-injected animals exhibited an average of 17.8 ±4.32 tumors/mouse at the dose level of 20 mg/mouse and 8.1 ±2.3 tumors at the dose level of 10 mg/mouse. Lungs were examined grossly and microscopically for abnormalities such as adenomatosis and inflammatory reactions, and none was reported. Except for one lymphoma and two salivary gland tumors seen in unspecified groups and described as spontaneous, no other unusual findings were cited.

According to Poirier et al [56], the absence of significant effects by benzyl chloride in mice was unexpected on the basis of known chemical activity and because of the injection-site sarcomas seen in rats by Druckrey et al [55]. Poirier et al [56] suggested that the difference may have been due to a greater metabolic inactivation of benzyl chloride in the liver by the ip route than by the sc route. Other important differences in experimental design were observed between these two investigations. The positive results reported by Druckrey et al [55] were observed in rats injected sc once a week for 51 weeks with a total dose of either 2.1 g or 3.9 g benzyl chloride/kg of body weight after a mean induction time of 500 days. In the 24-week study by Poirier et al, mice received only 8-12 ip injections during 8 weeks amounting to a total of 0.6-2.0 g of benzyl chloride/kg of body weight. Sufficient induction time for tumors may not have been allowed, although statistically significant increases in tumor induction occurred with 10 of the 17 alkyl halides tested.

McCann et al [57], in 1975, included benzyl chloride in a group of 23 chemicals that they used to evaluate two strains of Salmonella typhimurium, TA 100 and TA 98, recently derived as more sensitive indicators of

mutagenic potential. They apparently followed their standard "Ames test" procedure [58], without microsomal activation. After incubation for 48 hours at 37 C, colonies of histidine-independent revertants were counted and the results presented as revertant colonies/plate, after subtraction of spontaneous revertant values. The reported results were taken from the linear portion of the dose-response curve for each substance. Other dose levels tested and the number of plates prepared were not described.

For benzyl chloride at a dose of 2 mg/plate, 12 revertant colonies/plate were reported with test strain TA 1535, and 230 colonies/plate were reported with strain TA 100 [57]. Strain TA 1535 responds to base-pair substitution such as could occur following the alkylation of one of the bases of DNA. Strain TA 100 is made from strain TA 1535 with the addition of a plasmid (R factor) that may enhance damage to DNA by interfering with the recombinational repair system. No revertants were detected with strain TA 1538, which responds especially to frameshift mutagens. Bifunctional alkylating agents can cause DNA crosslinking, which could lead to frameshift mutations, but this would not be expected from a monofunctional alkylating agent like benzyl chloride. Twenty revertant colonies/plate were reported with strain TA 98, made from TA 1538 plus the R factor. The authors concluded that benzyl chloride was much more active as a mutagen in strain TA 100 than in its parent strain, TA 1535.

Later in 1975, these results were presented by McCann et al [59] in a tabulation of 300 chemicals, for which published reports of carcinogenicity in mammals were compared with the results of their Salmonella mutagenicity screening. In this evaluation, the authors defined "weakly mutagenic" as producing fewer than 0.10 revertants/nanomole of material tested. Benzyl chloride produced 0.02 revertants/nanomole and was thus classified as weakly mutagenic by the authors. However, inspection of the data obtained by the authors on other chemicals revealed that their "nonmutagenic" classification may range from fewer than 0.00001 revertants/nanomole to fewer than 0.25 revertants/nanomole. It appears that when benzyl chloride is tested in what is thought to be the most sensitive bacterial test system available, the results cannot be distinguished from those on "nonmutagens."

In 1976, Fluck et al [60] reported their results after testing a large number of chemicals, including benzyl chloride, in order to evaluate a bacterial system for screening potential mammalian carcinogens. The system utilized a repair enzyme-deficient (pol A-) mutant (P3478) of Escherichia coli that contained less than 1% of the DNA polymerase activity of its parent (pol A+) strain (P3110). This enzyme repairs altered DNA by excision of the defective portion of the molecule and catalyzes resynthesis of the correct sequence. The authors had postulated that chemicals that react with cellular DNA would be expected to decrease the growth rate of the mutant to a much greater extent than that of the parent.

Twenty-five µl of benzyl chloride was placed in the center well of each of two plates containing either the parent or the mutant strain [60]. Control plates of both strains were grown with ampicillin and colistin to check strain constancy and with dimethyl sulfate, which had consistently served as a (differential toxicity) positive control. All plates were incubated for 16 hours, presumably at 37 C. The zones of growth inhibition about the center wells then were measured in millimeters. A difference of 4 mm or more between parent and mutant strain was considered positive. The differential between the parent and mutant strain tested with benzyl chloride was 24 mm, ie, benzyl chloride apparently had a damaging effect on the DNA in this system.

The authors [60], however, concluded, on the basis of their data, that their test system would not be useful for routine prescreening of large numbers of compounds for carcinogenic potential. It did not distinguish between many known carcinogens and noncarcinogens, and it was not a quantitative assay in that a dose-response relationship was not seen and "potent" carcinogens did not necessarily show greater responses than did "weaker" ones.

Rosenkranz and Poirier, in a National Cancer Institute report [61] evaluating the degree of correlation between mutagenic and DNA-modifying activity in bacterial systems and carcinogenicity in animal tests, examined results of Ames and E. coli pol A tests with benzyl chloride. Salmonella strains TA 1535 and TA 1538 described above (but not the newer, more sensitive strains TA 98 and TA 100) were used in the Ames system. Each strain was exposed with and without the S-9 microsomal activation system at 10 µl benzyl chloride/plate and without activation at 5 µl/plate. In strain TA 1535, without activation, there were 43 revertants/plate at the 5 µl dose and 68 at 10 µl, contrasted with 22 revertants/control plate. The authors classified this result as "marginally positive." In both strains, control plates and those containing 10 µl of benzyl chloride and the S-9 system had 12 revertants/plate. The S-9 microsomal preparation had an inactivating effect on benzyl chloride at the 10 µl dose level, presumably because of the reaction of benzyl chloride with components of the S-9 system, probably protein.

Negative results were obtained on strain TA 1538 under the same experimental conditions. The authors noted that benzyl chloride is labile at 45 C , the temperature of top agar used in the Ames test, which could possibly have diminished its reactivity.

For the E. coli pol A assay, 10 µl benzyl chloride was added to the central disk of each plate. Each control and each dose level of benzyl chloride was tested in duplicate at least three times. The zone of inhibition was 16.3 mm in the pol A+ parent and 19.0 mm in the pol A- mutant; the difference of 2.7 mm was considered significant by the authors.

## Correlation of Exposure and Effect

Occupational exposure to benzyl chloride may occur by inhalation or by contact with the eyes or skin. Benzyl chloride is a powerful lacrimator and causes intense irritation of the upper respiratory tract as well [21,22,29,30]. The capacity of liquid benzyl chloride to damage the skin has been mentioned in the literature [27,62] but is not supported by any human case reports. However, because the molecule is highly reactive and capable of covalent bonding with nucleophilic groups such as are present in protein [7], and because hydrolysis of benzyl chloride releases hydrochloric acid, the potential for skin irritation by liquid benzyl chloride is consistent with these chemical (reactivity) considerations.

Human exposures to benzyl chloride vapor at 160-23,600 mg/cu m have been reported [21,22,27,29,30]. The longest exposure duration reported was only 5 minutes [29], presumably because of the intense irritation caused by the compound at concentrations as low as 88 mg/cu m [30]. At all concentrations in the range, the primary effect was an intense burning sensation in the eyes, accompanied by profuse tearing. At higher concentrations in the range, these effects were accompanied by conjunctivitis and respiratory irritation [21,22], described by Schutte as a catarrah [22], an inflammation of the mucous membranes of the head and throat. Watrous [27] described similar effects on the conjunctiva and respiratory tract after intermittent exposure to benzyl chloride at 2,590 mg/cu m.

Katz and Talbert [30] determined the ocular and nasal irritation thresholds of benzyl chloride. Intolerable eye irritation resulted from a 10-second controlled exposure to benzyl chloride at 410 mg/cu m. The threshold for nasal irritation was determined to be 180 mg/cu m, whereas that for eye irritation was determined to be 41 mg/cu m. In a 1971 summary report, for which documentation is not available, Mikhailova [29] stated that benzyl chloride at concentrations of 6-8 mg/cu m could result in slight conjunctivitis in workers after a 5-minute exposure.

The acute toxicity of benzyl chloride may not be limited to irritant effects on the eyes, respiratory mucosa, and skin. Animal studies have indicated that benzyl chloride, when inhaled at 100-23,600 mg/cu m, can induce acute pulmonary reactions [21,22,34]. Focal pulmonary hemorrhages were observed in rats exposed to benzyl chloride for 8 hours at 3,300 mg/cu m; however, exposures at 1,100 mg/cu m for 7.5 hours resulted only in pulmonary edema [21,22]. In animals exposed to benzyl chloride at 890 mg/cu m or greater for 6.8 hours, corneal turbidity was reported; however, this condition was reversible in 3 days [22]. When benzyl chloride was inhaled for 0.5 hours or more, at concentrations greater than 800 mg/cu m, an increased mucous secretion was consistently noted. Mikhailova [34], after exposing rats and mice for 2 hours to benzyl chloride at 100 mg/cu m, found hepatic changes that were described as albuminoid and fatty

degeneration. The fatty degeneration could possibly have included some fatty infiltration. Necrosis of the kidney, presumably a result of albuminoid degeneration of the convoluted tubular epithelial cells, was also reported. Workers exposed to benzyl chloride above 100 mg/cu m would probably exhibit similar reactions and may also be susceptible to secondary pulmonary infections. Moreover, workers with preexisting lung disease may be subject to an increased risk of further pulmonary damage.

Two studies [21,22] suggested that the irritant effects of benzyl chloride vapor may be cumulative. Schutte [22] initially exposed two cats to benzyl chloride at 2,000 mg/cu m for 0.5 hours and observed only lacrimatory effects, which ceased 0.5 hour after exposure ended. Reexposing the animals 5 days later at 800 mg/cu m for 0.5 hour resulted in similar lacrimatory effects; recovery was slower, however, and the animals died 3 weeks later of what was diagnosed as pneumonia. Wolf [21], who exposed two cats to benzyl chloride at 480 mg/cu m for 8 hours/day for 6 consecutive days, observed that the irritant effects of benzyl chloride appeared sooner each day, and with increasing severity, as the exposures continued.

Skin sensitization in guinea pigs exposed to benzyl chloride was tested by Landsteiner and Jacobs [35] in 1936. The animals were injected intracutaneously with 0.01 mg benzyl chloride in saline twice weekly for 12 weeks, then allowed to rest for 2 weeks prior to topical application of a benzyl chloride/olive oil suspension, whereupon an allergic-type skin response, manifested as erythema and swelling, was elicited.

Although no thorough studies of the metabolism of benzyl chloride in humans have been located, some inferences may be drawn from the available animal studies. In these cases, animals were exposed by various routes, and metabolic products in their urine were identified. In studies conducted with rats [37,41,42,44,63,64], rabbits [38,40,42,43], dogs [39], guinea pigs [46], and mice [53], benzylmercapturic acid was found to be a urinary excretion product. The percentage of administered benzyl chloride that was recovered as the product of its conjugation with glutathione, benzylmercapturic acid, varied from 49% in rabbits to 27% in rats and 4% in guinea pigs [41,46,65]. The enzymes which catalyze this conjugation of benzyl chloride with glutathione have also been isolated from human liver and show activity with benzyl chloride as substrate [32]. Another study [66] confirmed that humans are capable of forming mercapturic acids. It seems likely, therefore, that in humans benzyl chloride is excreted as benzylmercapturic acid.

## Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

The carcinogenic potential of benzyl chloride has been examined in two animal studies [55,56]. In a rat study [55], one group of 14, and another

of 8, animals received sc injections of benzyl chloride in peanut oil once weekly for 51 weeks at respective doses of 40 and 80 mg/kg/week. After a mean induction time of 500 days, injection-site sarcomas were identified in 3 of 14 rats administered the 40 mg/kg doses and in 6 of 8 rats administered the 80 mg/kg doses. No sarcomas were found in the vehicle-treated controls. Without further description, the authors stated that of the animals injected with the 80 mg/kg doses most had metastases to the lung, but that no lung metastases occurred at the 40 mg/kg doses. The authors stated that transplantation of the tumors was successful; however, no further descriptions were furnished.

The results of this study [55] indicate that benzyl chloride administered sc in peanut oil has a carcinogenic potential in rats. The weekly dosages administered amounted to 4-8% of the $LD_{50}$ for these animals. Local necroses occurred at the injection sites. The responses were dose related, ie, more injection-site sarcomas developed in animals given the higher dose, and lung metastases occurred only within the high-dose group.

Poirier et al [56] studied the carcinogenic activity of 17 low-molecular-weight alkyl halides including benzyl chloride. The production of lung adenomas in A/Heston strain mice was used as an indicator of the carcinogenic activity of these compounds. This strain has been shown to be sensitive to chemical carcinogens, as indicated by increased rate of lung adenoma formation. Benzyl chloride in tricaprylin was given in multiple ip injections at the MTD and at one-half and one-fifth the MTD. However, because of unspecified toxic effects the maximum dose subsequently was reduced, and all injections were given less frequently than originally planned (three times/week for 8 weeks). Total doses of 2,000 mg/kg, 1,500 mg/kg, and 600 mg/kg were administered in 8, 12, and 12 injections, respectively. All animals were killed 24 weeks after the initial injections; and lungs were removed, fixed, and examined. No significant increase in the incidence of pulmonary tumors was found in the benzyl chloride-injected mice compared with controls, probably, according to the authors, because the benzyl chloride was administered ip, enhancing the probability of metabolic deactivation of the injected material. In spite of the high rate of spontaneous tumorigenesis of the strain-A mice and the relatively short induction time, 10 of the 16 other low-molecular-weight monofunctional alkyl halides yielded positive results in this test system.

McCann et al [57] included benzyl chloride in a study in which 23 chemicals were screened for mutagenic activity in S. typhimurium strains TA 100 and TA 98, which are derived, by addition of a plasmid (R factor), from strains TA 1535 and TA 1538, respectively. For benzyl chloride at 2 mg/plate, 12 revertants/plate were reported with strain TA 1535 and 230 revertants/plate with the more sensitive TA 100. No revertants were reported with strain TA 1538, and 20 revertants/plate were reported with strain TA 98. The results of these tests were again published by McCann et

al [59] in a tabulation of the results of tests of 300 chemicals for mutagenic activity. In the report, benzyl chloride was classified as "weakly mutagenic," as defined by fewer than 0.10 revertants/nanomole. "Nonmutagenic" was not defined but appeared to range from fewer than 0.00001 revertants/nanomole to fewer than 0.25 revertants/nanomole.

Fluck et al [60], evaluating a repair enzyme-deficient E. coli test system for its potential as a carcinogen screen, included benzyl chloride as a test chemical. Benzyl chloride, 25 µl, was placed in the center well of each of two plates containing either the parent strain (pol A+) or the repair enzyme-deficient (pol A-) mutant. After 16 hours of incubation at 37 C, the difference in the zones of inhibition between the parent and mutant strains was 24 mm. This result was considered positive by the authors, who also concluded that the system was not useful as a routine prescreening test for carcinogens because it showed no dose-response relationship and could not distinguish between known carcinogens and noncarcinogens. The results of Fluck et al cannot be considered indicative of any purely mutagenic effects of benzyl chloride because differential growth may indicate effects other than specific alterations of the DNA molecule.

In a National Cancer Institute study, Rosenkranz and Poirier [61] tested several compounds, including benzyl chloride, in Salmonella and E. coli systems. Salmonella strains TA 1535 and TA 1538, described above, were tested with and without S-9 microsomal activation at 10 µl/plate, and without activation at 5 µl/plate. Without activation, there were 43 TA 1535 revertants/plate at the 5 µl dose and 68 at the 10 µl dose, compared with 12 spontaneous revertants/plate. With activation, both the control plates and those containing 10 µl of benzyl chloride had 12 revertants/plate. The S-9 microsomal preparation had an inactivating effect on benzyl chloride. This was presumed by the authors to have been caused by reaction of benzyl chloride with microsomal protein. Negative results were obtained with strain TA 1538 under the same experimental conditions. In a test system with repair enzyme-deficient E. coli, by the same authors, 10 µl of benzyl chloride added to the central disk of each plate resulted in zones of inhibition of 16.3 mm for the pol A+ parent strain, and 19 mm for the pol A- mutant. The authors proposed use of the TA 1535 and pol A tests in tandem as a screening technique for carcinogenic compounds. The data from strain TA 1535 are indicative of a dose-related effect. McCann et al [57], using benzyl chloride at 2 mg/plate, reported 12 revertants/plate. Rosenkranz and Poirier [61], using doses of 5 and 10 µl (5.5 and 11.0 mg), counted 43 and 68 revertants/plate, respectively.

No reports of teratogenic or reproductive effects associated with exposure to benzyl chloride have been found.

The results from experiments on bacteria and rodents indicate that benzyl chloride is a weak mutagen in microbial test systems and, following sc injection in rats, causes neoplastic changes at the injection site with

metastases. However, further animal research is required to estimate these risks following pulmonary exposure to benzyl chloride.

Data on the effects of exposure to humans and animals are presented in Tables III-2, III-3, and III-4.

TABLE III-2

SUMMARY OF EFFECTS OF EXPOSURE TO BENZYL CHLORIDE VAPOR IN HUMANS

| Concentration (mg/cu m) | Duration | Effects | Reference |
|---|---|---|---|
| 0.21-0.24 | Brief* | Odor thresholds | 30,31 |
| 6-8 | 5 min | Conjunctivitis | 29 |
| 41 | 10 sec | Eye irritation threshold | 30 |
| 180 | One breath* | Nasal irritation threshold | 30 |
| 160-17,700 | Brief* | Lacrimation, conjunctivitis, respiratory tract irritation | 21 |
| Up to 2,590 | Intermittent* | Conjunctivitis, upper respiratory tract irritation | 27 |
| 800-23,600 | Brief | Eye and respiratory irritation | 22 |

* Authors' description

TABLE III-3

SUMMARY OF EFFECTS OF BENZYL CHLORIDE VAPOR ON ANIMALS

| Species* | Concentration (mg/cu m) | Duration | Effects | Reference |
|---|---|---|---|---|
| Mouse | 2,000 | 1 hr | All survived | 33 |
| " | 390 ($LC_{50}$) | 2 hr | Respiratory tract inflammation, secondary infection | 34 |
| Rat | 2,000 | 1 hr | All survived | 33 |
| " | 740 ($LC_{50}$) | 2 hr | Respiratory tract inflammation, secondary infection | 34 |
| " (10) | 100 | " | Weight loss, eye and respiratory tract irritation | 34 |
| Rabbit (1) | 480 | 8 hr/d for 6 d | Mild eye irritation, reddening of oral and nasal mucosa by 6th d | 21 |
| Cat (2) | 480 | " | Eye and respiratory tract irritation, loss of appetite | 21 |
| Dog | 1,900 | 8 hr | Irritation of the ocular, respiratory, and oral mucosa, corneal turbidity, death within 24 hr | 22 |

* Numbers in parentheses represent the number of animals.

TABLE III-4

SUMMARY OF EFFECTS OF BENZYL CHLORIDE ON ANIMALS

| Route of Administration | Species* | Concentration (mg/kg) | Regimen | Effects | Reference |
|---|---|---|---|---|---|
| oral | Mouse | 1,624 | -- | 50% died | 33 |
| " | Rat | 1,231 | -- | " | 33 |
| sc | " | 1,000 | -- | " | 55 |
| " | " (8) | 80 | 1/wk, 51 wk | Six developed local sarcomas with mean induction time of 500 d, most with lung metastases. | 55 |
| " | " (14) | 40 | " | Three developed local sarcomas with mean induction time of 500 d; no metastases reported. | 55 |
| ip | Mouse (20) | 250 | 8 injections within 8 wk | No significant increase in lung adenomas by 24th wk | 56 |
| " | " | 125 | 12 injections within 8 wk | " | 56 |
| " | " | 50 | 12 injections | " | 56 |
| intracutaneous followed by dermal | Guinea pig | 0.01 mg in saline solution followed by application of liquid to skin | 2/wk for 12 wk to sensitize; dermal application 2 wk later | Skin swelling and pinkness | 35 |

* Numbers in parentheses represent numbers of animals exposed.

## IV. ENVIRONMENTAL DATA AND ENGINEERING CONTROLS

### Environmental Data

NIOSH has conducted industrial hygiene surveys of several facilities engaged in the manufacture or use of benzyl chloride [10]. A summary of data collected by personal monitoring at two facilities is presented in Table IV-1. Workplace area concentrations of benzyl chloride were determined using organic vapor and infrared analyzers. Personal samples were collected in charcoal tubes with subsequent solvent desorption and analysis by gas-liquid chromatography and a flame ionization detector. The average 8-hour time-weighted benzyl chloride concentrations related to various work operations were assessed by personal sampling in two plants. The results indicated good precision and accuracy for both the collection and analysis of benzyl chloride, alone or in combination with toluene, a contaminant frequently found in the manufacturing area [10]. These values ranged from 0.01 to 0.14 ppm (0.05 to 0.73 mg/cu m) in one plant and from 0.01 to 0.08 ppm (0.05 to 0.41 mg/cu m) with the exception of one TWA concentration of 3.19 ppm (16.5 mg/cu m) during an instance of facility malfunction in the second plant. Compared to the current Federal TWA limit of 1 ppm (5 mg/cu m), the concentrations found were not regarded as excessive.

An earlier report [67] presented the results of air sample analysis from various points in a benzyl alcohol production facility in the Soviet Union. The highest concentrations of benzyl chloride (0.8-8.0 mg/cu m) were measured at the quality control sampling outlet of the reactor. Measurements obtained during quality control sampling at the level of inhalation 1.5 m from the apparatus, ranged from 0.3 to 2.0 mg/cu m. Sampling at the seal of the mixing apparatus and at the ventilation intake grid also gave relatively high readings (0.66-1.4 mg/cu m and 0.67-1.3 mg/cu m, respectively), possibly because the intake shaft was located close to the benzyl chloride exhaust vent. All samples taken 1.5 m from the apparatus or grid, at inhalation level, contained 0.5 mg/cu m or less.

### Sampling and Analytical Methods

#### (a) Direct-Reading Instruments

No direct-reading instruments are available that would specifically measure airborne benzyl chloride concentrations. Two direct-reading organic vapor analyzers (OVA's) were used in a study of the benzyl chloride levels in two chemical plants [10]. The investigators used one OVA, equipped with a flame ionization detector, to measure the general levels of organic vapors, including benzyl chloride. However, this type of

TABLE IV-1

BENZYL CHLORIDE CHARCOAL COLLECTION TUBE
AIR SAMPLING RESULTS--PERSONAL MONITORING

| | Job Title | Mean Exposure Time (min) | Mean Vol (liters) | Mean Concentration (ppm) | (mg/cu m) |
|---|---|---|---|---|---|
| A* | Benzyl chloride chief operator (2)** | 319 | 83 | 0.07 | 0.36 |
| B | Benzyl chloride chief operator (7) | 440 | 108 | 0.03 | 0.16 |
| A | Benzyl chloride operator (3) | 412 | 108 | 0.10 | 0.52 |
| B | Benzyl chloride operator (7) | 442 | 116 | 0.04 | 0.21 |
| A | Benzyl chloride drumming (2) | 408 | 99 | 0.03 | 0.16 |
| B | Benzyl chloride material handling (4) | 248 | 62 | 0.03 | 0.16 |
| A | Benzyl chloride maintenance (3) | 360 | 94 | 0.09 | 0.47 |
| B | Benzyl chloride maintenance (1) | 275 | 63 | 0.01 | 0.05 |
| A | Benzyl alcohol operator (4) | 410 | 102 | 0.02 | 0.10 |
| A | Benzyl cyanide operator (12) | 387 | 100 | 0.02 | 0.10 |
| B | Crude plasticizer operator (7) | 446 | 112 | 0.03 | 0.16 |
| B | Refining plasticizer operator (7) | 445 | 110 | 0.03 | 0.16 |
| A | Quality control sampling (1) | 13 | 4 | 0.27 | 1.40 |
| B | Quality control sampling (2) | 21 | 6 | 0.10 | 0.52 |
| A | Quality control sampling (toluene stripper) (1) | 33 | 8 | 0.02 | 0.10 |
| B | Drum filling (1) | 25 | 7 | 0.02 | 0.10 |

*A or B refers to plant sampled.
**Number in parentheses = number of samples.

Adapted from reference 10

detector has a much lower sensitivity to benzyl chloride, and to any other chlorinated compounds, than it has for hydrocarbons. The other OVA, equipped with an infrared detector, was used to record the concentration of benzyl chloride at a single location continuously.

A new type of OVA, based on ultraviolet photoionization principles, reportedly offers potential for instantaneous measurement of benzyl chloride vapor in the 0.1- to 700-ppm (0.5 to 3,660 mg/cu m) range. There is said to be no lowering in sensitivity due to the chloride. NIOSH has not yet tested this instrument.

A colorimetric detector tube is available that is capable of indicating the presence of benzyl chloride in the 1-10 ppm (5-50 mg/cu m) range [68]. The reaction used is not specific for benzyl chloride because it is based on oxidation by potassium permanganate and fixation of the liberated chlorine with o-tolidine, resulting in a colored product. Other chlorinated chemicals would react similarly. In the presence of other organic vapors, such as ethylene, butadiene, and heptane, some permanganate is consumed, thereby reducing the sensitivity of the method.

Within the limits of their sensitivities, direct-reading instruments might be useful for monitoring areas where benzyl chloride is known to be present, such as in a drumming operation, by warning of imminent hazards, leaks, and control system malfunctions. Some instruments can measure rapidly fluctuating levels. Direct-reading instruments are portable and give immediate results.

(b) Sampling

Liquid absorbents can be used to trap benzyl chloride vapor, and the collected sample can be directly analyzed by colorimetry. An ammonium nitrate solution has been used to collect benzyl chloride in air [69], in the absence of benzene and other aromatics, and in the presence of aliphatic halides. A similar method using pyridine [69] was unaffected by aromatics, but halogenated compounds did interfere. The collection system using pyridine must be kept at 6 C by use of a salt/ice bath, a requirement that limits its use to area sampling. Another report [70] discussed the use of a pyridine-formalin mixture as the absorbing medium, in conjunction with analysis by the Fuziwara reaction. Absorption of benzyl chloride in quinoline has been reported [71] to permit its subsequent colorimetric analysis, even when collected in the presence of benzal chloride and benzotrichloride. To eliminate interference by chlorine in this sampling system, a prefilter made up of two sections of cotton, impregnated respectively with potassium iodide solution (10%) and sodium thiosulfate solution (10%), was used upstream from the absorber.

Organic vapors, including benzyl chloride, were collected near a chlorination plant [72] in absorption tubes containing a granular support

of Celite 545 with a stationary phase made of silicone elastomer E301. The collected samples were thermally desorbed directly into a gas chromatographic column. Tests with air containing 1 ppm of benzyl chloride have shown a collection efficiency of 80-100% in the presence of other chlorinated toluene products at 1 ppm and of toluene at 100 ppm. Under similar conditions, silica gel was shown to absorb benzyl chloride so strongly that even after 5 minutes of heating it could not be desorbed.

Activated charcoal is an excellent collection medium because of its nonpolarity and its affinity for organic vapors and gases. Adsorption and desorption efficiencies may vary, however, with different batches of charcoal, so that it is necessary to determine the desorption efficiency (DE) for each new batch of charcoal [73]. In the recommended charcoal tube sampling method [73], a known volume of air is drawn through charcoal to adsorb benzyl chloride. A personal sampling pump with flowrate set at 0.2 liters/minute is used to collect the samples. Appropriate blanks also are prepared. When two or more components are known or suspected of being present, provision of information on the identity of the suspected additional components is required. NIOSH has validated this method [74].

(c) Analysis

Benzyl chloride may be determined quantitatively by colorimetric procedures [69,75]. In one method [69] benzyl chloride is determined after its nitration to 2,4-dinitrobenzyl chloride, and its extraction with methyl ethyl ketone followed by alkalinization with potassium hydroxide. The resulting violet color is measured spectrophotometrically at 570 nm. This method requires at least 40 µg of benzyl chloride, equivalent to sampling 8 liters of air containing benzyl chloride at a concentration of 5 mg/cu m. A similar method employs pyridine heated with sodium hydroxide to yield a yellow-orange color, which is measured spectrophotometrically at 430 nm. It requires at least 0.1 mg of benzyl chloride, equivalent to sampling 20 liters of air at the recommended ceiling concentration.

A third method, useful for the quantitative determination of benzyl chloride in the presence of benzal chloride and benzotrichloride [71], employs a reaction with quinoline, a tertiary amine, to form basic quaternary quinolinium salts. When heated, these salts form yellow cyanine dyes that are spectrophotometrically separable in the ultraviolet range; however, absorbance spectra were not reported. This method was reported to be sensitive to benzyl chloride at 1 µg/ml of sample solution. Benzal chloride and benzotrichloride interfered with the analysis when present in the sample solutions at concentrations greater than 25 µg/ml and 250 µg/ml, respectively. Sampling at a rate of 0.2 liter/minute for 15 minutes would be sufficient to determine benzyl chloride at 1 mg/cu m.

In a method that has some potential, but has not yet been tested in an industrial setting, benzyl chloride samples are collected in a 9:1

pyridine-formalin solution; sodium hydroxide solution is added, and the resulting color measured spectrophotometrically [70]. The presence of formalin stabilized the color, which is measured at 370 nm.

Benzyl chloride also has been determined in air using its ultraviolet and infrared absorption characteristics [71,76]. Calibration curves for benzyl chloride [71] in ethanol indicate that there is a linear relationship between optical density and concentration in the range of 1-15 μg/ml of sample. Long-path infrared analysis is subject to broad-band absorption interferences by water vapor and carbon dioxide, at levels near the recommended ceiling concentration limit. One report [76] estimated that the detection limit for benzyl chloride measured in dry air at 10 atm pressure at 1,269 $cm^{-1}$ (7.88 μm) is 0.8 ppm (4 mg/cu m).

Several gas-liquid chromatographic techniques [72,74,77-81] have been described for the determination of benzyl chloride. These methods must be selected and adjusted for the particular conditions at hand. When other substances are present that may interfere because of similar retention times, it may become necessary to make several determinations using different separation conditions (column packing, column temperature programming, etc) [74]. Benzyl chloride may be analyzed by comparison with appropriate internal standards including carbon tetrachloride [77], tetradecane [82], and n-heptadecane [73].

Gas chromatographs equipped with flame ionization detectors are capable of simultaneous separation and quantitative measurement of selected compounds found in industrial solvent vapor mixtures [80]. Such methods are efficient and accurate. The recommended method [73] for benzyl chloride analysis is an adaption of method No. S-115 that was validated by NIOSH in the range of 2-8 mg/cu m for a 10-liter air sample [74]. The working range of the method is 1.7-50 mg/cu m. By slight modification of the sample collection, preparation, and analytical techniques, it would be possible to detect lower concentrations of benzyl chloride. The compound is extracted from the charcoal using carbon disulfide, and a suitable aliquot is injected into a gas chromatograph equipped with a flame ionization detector. The liquid medium allows multiple gas-liquid chromatographic analyses to be made from one sample [80]. The selectivity of the gas-liquid chromatographic method is sufficient to allow separation of benzyl chloride from other substances that typically may be present, such as toluene, benzaldehyde, benzal chloride, benzotrichloride, and benzoyl chloride. These separations are discussed in detail in several reports [72,77-79,81,82].

Considering the ease of collection, the stability of the sample, and the specificity and sensitivity of the analytical method, the combination of charcoal tubes and gas-liquid chromatography constitutes the preferred

method for monitoring benzyl chloride in the industrial environment. Other methods can either provide similar results, or offer the convenience of direct reading, or require only a minimum of investment in equipment. Choices will be dictated by the specific problems of monitoring in any given industrial environment. The recommended charcoal tube sampling and gas-liquid chromatographic analytical methods are described in detail in Appendix I (Chapter IX). When performing benzyl chloride analyses by the recommended method, one must exercise extreme caution at all times because of the toxicity and fire and explosion hazards of carbon disulfide. It can be ignited by hot steam pipes. All work with carbon disulfide must be performed under an exhaust hood.

## Engineering Controls

The manufacture of benzyl chloride and its use in a variety of organic synthetic processes are generally performed in closed systems [83]. However, when closed systems are not practical or when leaks develop, workplace exposure to benzyl chloride is possible. The likelihood of exposure increases during handling, transferring, or sampling operations.

A local ventilation or exhaust system may be necessary when benzyl chloride is not used in closed systems. The principles set forth in NIOSH's Recommended Industrial Ventilation Guidelines [84], Industrial Ventilation--A Manual of Recommended Practice [85], and Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971 [86] should be applied to control atmospheric concentrations of benzyl chloride during those operations when exposure is possible. A flexible local exhaust system, consisting of an 8-inch flexible duct and a 24-inch hood exhausting air at 2,300 linear feet/minute positioned 10 inches above a drum being filled with benzyl chloride, was used to capture vapor emitted from the bunghole of the drum [83]. In another application of local exhaust ventilation during a drum-filling operation, a 4-inch flexible tubing exhausting air at 800 linear feet/minute, also captured vapor being emitted from the bunghole [10]. In transfer of benzyl chloride to or from tank trucks or similar vessels, prevention of spills can be accomplished by purging all lines with nitrogen gas before disconnecting delivery lines. When benzyl chloride is handled in open systems, adequate ventilation is essential to protect employees from potential exposures. Ventilation systems require inspection and maintenance on a regular basis to ensure effective operation. Routine inspection should include face velocity and static pressure measurements of the collecting hood, examination of the air mover and collection or dispersion system, and measurements of atmospheric concentrations of benzyl chloride in the work environment. Any changes in the work operation, process, or equipment that may affect the ventilation system must be promptly evaluated to ensure that control measures provide adequate protection of employees.

In the presence of moisture, benzyl chloride slowly hydrolyzes, forming benzyl alcohol and hydrochloric acid. All facilities require frequent inspection and preventive maintenance to ensure that leaks are detected and repaired to avoid exposure of employees. Piping, exhaust system components, reactor vessels, storage vessels, and containers for benzyl chloride must be made from materials that are corrosion resistant. Most vessels and piping should be fabricated from nickel or high-nickel steel, or lined with glass, lead, or phenolic material. Benzyl chloride readily decomposes in the presence of iron, copper, zinc, aluminum, and various alloys containing these metals. If this reaction occurs in a closed container, benzyl chloride can undergo an exothermic polymerization reaction possibly leading to an explosion. One chemical plant that produced benzyl chloride was destroyed by an explosion and fire [87]. Storage of benzyl chloride requires that measures be taken to exclude water. One technique is to vent storage tanks through a tube containing anhydrous calcium chloride or a similar desiccant. Decomposition and polymerization can be prevented by use of propylene oxide to inhibit the formation of free radicals and to scavenge any hydrochloric acid that may be produced. The useful storage life for benzyl chloride is about 3 months [14].

# V. WORK PRACTICES

Work and sanitation practices appropriate to the manufacture, handling, and use of benzyl chloride should be primarily concerned with preventing the inhalation of its aerosol or vapor and preventing skin and eye contact with the liquid. Work practices also are concerned with controlling hazards associated with the raw materials, chlorine and toluene, used in the production of benzyl chloride, and with process byproducts including hydrochloric acid, benzal chloride, and benzotrichloride.

## (a) Protective Clothing and Equipment

Protective clothing and chemical safety goggles should be worn by employees subject to skin or eye contact with benzyl chloride. Such protection is particularly important while collecting samples, filling drums and tanks, making process adjustments, or maintaining equipment where it is possible to come into contact with irritating liquids or vapors. Protective clothing should be made of material resistant to benzyl chloride. Gloves made of natural rubber, neoprene, or plastic should be worn by employees when they are handling irritant substances, although the permeability of these materials to benzyl chloride remains to be determined. Aprons and boots of rubber or other appropriate materials are recommended for added protection during material handling and usage operations.

Personal protective clothing, devices, and equipment should be cleaned and inspected on a regular schedule, and replaced when worn or broken. Clothing heavily contaminated with benzyl chloride must be removed immediately, and the employee must shower. A laundry service provided by the employer is recommended for the cleaning of contaminated work clothing. Such service would avoid the risk of carrying benzyl chloride or other irritants into the home environment. Plant personnel involved in laundering should be apprised of the hazards associated with the handling of benzyl chloride. If an outside laundry facility is used, the laundry employer must be advised of the hazards involved in handling clothing contaminated with benzyl chloride and of the requirements to ensure that the laundry employees are not exposed to benzyl chloride. Protective clothing should be stored separately from street clothing in lockers with separate compartments provided for that purpose.

In order to ensure that employee exposure does not occur while engineering controls are being installed or altered, respiratory protective devices as specified in Chapter I must be used during this time. Respiratory protective equipment is not an acceptable substitute for proper engineering controls but should be available in emergencies and for nonroutine maintenance and repair situations.

(b) Sanitation

According to the National Fire Protection Association, benzyl chloride has a lower flammable limit in air of 1.1% by volume, with an autoignition temperature of 585 C [88]. Therefore, smoking must not be permitted where benzyl chloride is manufactured, used, handled, or stored. Use of matches, lighters, or other sources of ignition should be restricted to designated areas. Because benzyl chloride is very irritating to the skin and mucous membranes, eating facilities should be separated from work areas. Employees should follow rules of good personal hygiene. They should wash their hands before smoking, eating, or using toilet facilities. A supply of potable water should be available near all places where there is a potential for contact with benzyl chloride or its irritant derivatives. A water supply may be provided by a free-running hose at low pressure or by emergency showers. Where contact with the eyes is likely, eyewash fountains should be readily available.

(c) Spills and Waste Disposal

Spills and leaks of benzyl chloride can result in the presence of its vapor at hazardous concentrations. Leaks should be stopped and repaired as soon as possible after detection. Each employee engaged in cleanup operations must wear protective equipment and clothing. The objective is to confine a spill to as small an area as possible to avoid needless exposure of employees.

Unless necessary to prevent a fire, benzyl chloride should not be flushed with streams of water, which may disperse the material over a wide area, although water fogs or sprays may be useful to contain the spread of vapor. However, dikes around storage areas and holding ponds for benzyl chloride runoff may make flushing of spills with water practical. Contaminated water may be pumped into holding tanks where the benzyl chloride will slowly hydrolyze to benzyl alcohol and hydrochloric acid. Benzyl chloride should be treated with an alkali such as lime, soda ash, or sodium bicarbonate prior to disposal of wastes to receiving waters or treatment plants.

Large spills should be diked with sand, earth, or other suitable absorbent material. Evolution of benzyl chloride vapor may be quickly suppressed by covering a spill with a foam, which may be followed by hydrolysis and neutralization of hydrochloric acid with alkali. Foam application may be followed by vermiculite or other suitable absorbents. Such absorbents also may be applied directly to spills. Hexamethylene tetramine has been reported to be a rapid and effective neutralizer of benzyl chloride and may be used directly on spills as an aqueous (30-40%) solution. Within a few minutes, a water-soluble quaternary salt, benzyl hexamethylene tetrammonium chloride, forms [83]; it is said that this is safe to handle and that it may be flushed away with water. In the presence

of strong bases or acids, the quaternary salt would hydrolyze to benzylamine or to benzaldehyde, respectively (Sommelet reaction 89 ). Certain materials that will not absorb water but will absorb organic materials may be used for cleanup of spills of benzyl chloride mixed with water. Other materials that nonselectively absorb all liquids may be used when the spill is not mixed with water. After the sorbent materials have been applied, a firefighting foam may be used to cover the entire spill area. The solid sorbents used in cleanup of a spill should be packed into polyethylene-lined drums for subsequent disposal at a Class I landfill site 90 . Filled waste containers should not be allowed to accumulate and should be disposed of frequently. Methods of waste disposal must comply with Federal, state, and local regulations.

(d) Housekeeping and Maintenance

As stated previously, benzyl chloride is corrosive in the presence of traces of water; therefore, equipment for its manufacture and use must be maintained and regularly inspected. Leaking seals should be replaced, and leaking tanks and pipes should be repaired as soon as possible to reduce the possibility of worker exposure and loss of products or other materials. Special precautions are needed to prevent employees from being exposed during maintenance and repair operations. Procedures for draining and flushing lines should be established, and adequate local ventilation should be available. Each employee should wear sufficient personal protective equipment and clothing to prevent skin and eye contact and to minimize inhalation exposure.

Maintenance and repair workers, especially those working on ventilation systems or in enclosed environments, have a high risk of exposure to benzyl chloride and associated chemicals. To minimize or prevent exposure, they must be familiar with the hazards of the materials and with proper work practices, and they must have adequate supervision. Special precautions must be taken when work is to be performed in confined spaces. Entry into confined spaces should be controlled by a permit system. Prior to entry, all sources of benzyl chloride must be sealed off, and the equipment used for handling benzyl chloride must be purged and tested for oxygen deficiency and for the presence of flammable vapors and toxic gases. Purging should be done with nitrogen and followed by flushing with water. Continuous ventilation of the confined space should be maintained throughout the entry period. Personnel entering confined spaces should wear protective clothing, be equipped with a safety harness and lifeline, and use either a self-contained breathing apparatus in pressure-demand mode or a combination supplied-air suit with an auxiliary self-contained air supply. Anyone entering a confined space should be observed by a properly trained and equipped standby worker familiar with emergency procedures, should rescue become necessary. A communication system should be set up among workers involved in the operation. Adherence to good housekeeping and maintenance procedures and practices should minimize fire, accident,

and chemical exposure hazards. All equipment should be cleaned on a routine basis to avoid buildup of wastes. To minimize the spread of fire, should one occur, the grounds surrounding work areas should be kept clear of combustibles such as trash and vegetation.

(e) Storage, Handling, and Transportation

Benzyl chloride should be transported and stored in sealed, intact containers. A sealed container is one that has been closed and kept closed to the extent that there is no release of benzyl chloride. An intact container is one that has not deteriorated or been damaged to the extent that benzyl chloride is released. Sealed, intact containers pose no threat of exposure to employees; therefore, it should not be necessary to comply with required monitoring and medical surveillance requirements in operations involving such containers. If, however, containers are opened or broken so that benzyl chloride may be released, then all provisions of the recommended standard should apply.

Benzyl chloride should be kept dry and stored away from direct sunlight or heat and from oxidizing agents. Hydrolysis of benzyl chloride occurs slowly in the presence of moisture but is accelerated by heat. Hydrogen chloride gas released by this reaction may build up to a dangerous pressure. Excessive heat will also cause decomposition of benzyl chloride, releasing toxic vapors and fumes that also could build up to explosive pressures.

Inside storage rooms for benzyl chloride should be constructed in accordance with the requirements of 29 CFR 1910.106. Storage areas should be inspected frequently. Containers of benzyl chloride should be properly labeled. Warning labels indicating the nature of eye, respiratory, and skin irritation hazards must be affixed to any container used to transport or store benzyl chloride. Containers should be opened carefully to avoid release of material due to pressure buildup. Signs should be posted in areas where the material is stored or handled to provide safety and hazard information, exit locations, and requirements for respiratory or other protection. Exits from storage areas should be easily accessible and clearly marked.

Damaged drums should be emptied promptly. The iron from damaged drum linings or bung threads can catalyze reactions leading to a dangerous buildup of hydrogen chloride gas. The storage life of benzyl chloride is only 2-3 months due to the possibility of exhaustion of the inhibitors added to neutralize hydrogen chloride and to scavenge free radicals. Care should be taken, therefore, to rotate supplies of benzyl chloride so that storage time does not exceed shelf life.

Benzyl chloride should be loaded and unloaded only in areas where adequate ventilation can be provided. These operations should be conducted away from any source of heat, flame, or sparks.

(f) Emergency Procedures and First Aid

Drills and instructions in emergency procedures and evacuation should be integral parts of work operations. Employers and employees should continually evaluate and, as necessary, update procedures. Employers should provide all necessary emergency equipment and ensure that it is clearly marked, readily accessible, and maintained in working order; employees and supervisors should know the location of emergency shutoff valves. Full protective clothing including boots and self-contained breathing apparatus should be kept in marked and readily accessible locations.

Emergency showers and eyewash fountains should be located near benzyl chloride work areas. In case of skin or eye contact, the employee should immediately wash the skin thoroughly or flush the eyes with copious amounts of water. Employees should be cautioned against touching or rubbing their eyes while working with benzyl chloride. Heavily contaminated clothing and shoes should be removed at once.

Fires involving benzyl chloride can release toxic gases such as phosgene, hydrogen chloride, and carbon oxides. Employees especially trained in firefighting techniques should be available on each shift. Firefighters should use protective equipment including goggles and self-contained breathing apparatus. Streams of water may serve to disperse benzyl chloride over a wider area; however, water spray or fog, foam, carbon dioxide, or dry chemical extinguishment may be employed. Water spray is effective in dispersing combustion products.

Local fire units and rescue squads should be apprised of the types of emergencies anticipated in the plant. Phone numbers for such emergency assistance must be prominently posted in areas where emergencies might occur.

Alarm systems to alert plant personnel to emergency situations are recommended. Such alarm systems could also be used to signal firefighting teams.

First-aid services should be available, and there should be established procedures for obtaining first aid. Properly trained and qualified individuals should be available to administer first aid. Transportation services to move injured employees to hospitals, clinics, or physicians' offices should be prearranged and understood by supervisors and first-aid personnel. These procedures should be periodically reviewed and, as necessary, updated.

The effectiveness of work practices depends on the knowledge and informed cooperation of employees and employers. Employers must take steps to ensure that: (1) each employee receives adequate instruction and

training in safe work procedures, the proper use of all equipment appropriate to the workplace, the proper use of personal protective equipment and clothing, and emergency procedures; (2) each employee periodically receives refresher sessions and drills in order to maintain safe work practices and emergency procedures; and (3) each employee is provided with proper tools and equipment.

# VI. DEVELOPMENT OF STANDARD

## Basis for Previous Standards

In 1955 [91], the American Conference of Governmental Industrial Hygienists (ACGIH) proposed, and in 1956 [92] adopted, a threshold limit value (TLV) of 1 ppm (approximately 5 mg/cu m) as an 8-hour TWA exposure limit for benzyl chloride.

According to the Documentation of Threshold Limit Values for Substances in Workroom Air [93], this TLV was based in part on data summarized from earlier work [21,22,24] by Flury and Zernik [25], who stated that a 1-minute exposure to benzyl chloride at 16 ppm (83 mg/cu m) was intolerable to humans, and that an 8-hour exposure at 170 ppm (881 mg/cu m) was life threatening to cats. The TLV was also based on comments by Smyth [28] concerning the irritating effects of benzyl chloride on the eye, nose, and throat. Smyth stated: "The 1 ppm threshold limit...is undoubtedly low enough to prevent lung injury." There has been no change in either the recommendation or the TLV documentation since its adoption.

The present Federal standard (29 CFR 1910.1000) for exposure to benzyl chloride in the occupational environment is 1 ppm (5 mg/cu m), expressed as an 8-hour TWA limit, based on the ACGIH recommendations.

Argentina, Great Britain, Norway, and Peru have adopted the US Federal standard [94]. A Maximum Allowable Concentration (MAC) of 5 mg/cu m (1 ppm) has been adopted by Finland, Federal Republic of Germany, Rumania, and Yugoslavia [95]. The MAC for benzyl chloride vapor in the USSR was reduced in 1964 from 50 to 0.5 mg/cu m and has remained unchanged [67].

## Basis for the Recommended Standard

### (a) Permissible Exposure Limit

Employees exposed to benzyl chloride vapor may experience conjunctivitis [21,27,29] or immediate eye irritation, manifested as a burning sensation and tearing [21,22]. Lung damage and reversible corneal opacity have been reported in animals after 6-8 hour exposures above 800 mg/cu m, concentrations that would be encountered only in emergency situations, [21,22]. The mucous membranes of the nose and upper respiratory tract also may be irritated by benzyl chloride vapor at 180 mg/cu m or above [21,30,96]. The human eye irritation threshold for benzyl chloride vapor has been determined to be 41 mg/cu m for a 10-second exposure [30]. Slight conjunctivitis has been reported in workers after 5 minutes (300 seconds) at 6-8 mg/cu m [29]. Despite the absence in this

study [29] of information relating to sampling and analytical methods, to the number or percentage of workers affected, or to possible exposures to other chemicals, the results compare well with those obtained in a controlled laboratory study [30].

The mutagenic potential of benzyl chloride has been investigated in two bacterial test systems [57,59,60]. In the "Ames" test, McCann et al [57,58] classified benzyl chloride as "weakly mutagenic," defined as causing fewer than 0.1 revertants/nanomole. "Nonmutagenic" and "weakly mutagenic" compounds, however, could not be distinguished from one another based on the data and definitions used. Rosenkranz and Poirier [61], whose data generally agree with those of McCann et al, stated that addition of hepatic microsomal activating preparations to the test plates consistently led to negative results in both strains tested, presumably, according to the authors, because of a reaction between benzyl chloride and microsomal protein. Fluck et al [60], using the same E. coli system used by Rosenkranz and Poirier [61], presented data indicative of a nonspecific DNA-modifying effect, as measured by growth inhibition. The results of these studies are only suggestive of a mutagenic potential of benzyl chloride.

Benzyl chloride also has been screened for carcinogenic potential in mice and rats [55,97]. Druckery and coworkers [55] reported that injection-site sarcomas developed in 3 of 14 and 6 of 8 rats administered 51 weekly sc injections of benzyl chloride in peanut oil at 40 mg/kg and 80 mg/kg, respectively. Lung metastases, not further characterized, were found in most of the rats that developed sarcomas after the 80-mg/kg doses. Poirier et al [56], however, giving repeated ip injections of benzyl chloride in tricaprylin at 250 mg/kg, 125 mg/kg, and 50 mg/kg for 8, 12, and 12 injections, respectively, did not find a significant increase in pulmonary adenomas in A/Heston strain mice. The lack of an enhanced rate of pulmonary tumor formation may have been due to the expected differences in rates of absorption and metabolism for benzyl chloride between the sc and ip routes. The screening system used by Poirier et al appears to have some validity, however, since 10 of 16 other low molecular weight alkyl halides tested yielded positive results within the 24-week duration of the study.

Benzyl chloride is a highly reactive chemical that can alkylate in vivo, as confirmed by its rapid conjugation with glutathione in many animal species [41,51,64]. The primary conjugation product, S-benzyl glutathione, is a stable molecule that can, however, be enzymatically degraded. Conjugation essentially terminates the alkylating capability of benzyl chloride and, in mammals, leads to the excretion of the compound as benzyl mercapturic acid [38-40]. An in vitro study by Suga et al [64] indicates that conjugation with glutathione can occur both enzymatically and nonenzymatically in rat liver preparations. The enzymic conjugation reaction is also known to occur in human liver preparations [32] and may

also occur in a variety of other human tissues as it does in various animal tissues [41]. The enzymic reaction rate between benzyl chloride and glutathione in human liver was determined to be 0.5 micromoles of thiol lost/minute/g of tissue; therefore, the calculated conjugating capacity of the 1.5-kg human liver for benzyl chloride is approximately 721 micromoles/minute. For this capacity to be exceeded, an airborne benzyl chloride concentration of 5,700 mg/cu m would be necessary, assuming 100% absorption of the vapor.

The presently available data are deemed insufficient upon which to base a firm conclusion as to the carcinogenic and mutagenic potentials of benzyl chloride in occupationally exposed workers. However, the evidence of an efficient detoxification mechanism [32,38-43] suggests that the risk of effects from chronic low-level exposure to benzyl chloride is exceedingly small, probably negligible. The principal effects against which the worker must be protected, and upon which the recommended standard should be based, are the acute irritant effects. The lowest exposure to benzyl chloride reported to induce mild irritant effects in humans is 6-8 mg/cu m for a period of 5 minutes [29]. The present Federal occupational standard (a TWA limit of 5 mg/cu m) allows excursions in excess of the lowest concentrations of airborne benzyl chloride known to produce irritant effects in workers. In order to prevent such excursions, NIOSH recommends a ceiling concentration of 5 mg/cu m based on a 15-minute sampling period. In actual practice, a 15-minute ceiling of 5 mg/cu m is probably equivalent to a significantly lower TWA concentration, perhaps 1-3 mg/cu m. The recommended limit should adequately protect workers from the acute adverse effects of benzyl chloride and also markedly reduce any potential for long-term adverse effects.

(b) Sampling and Analysis

The technology is currently available to sample and analyze for benzyl chloride at the recommended ceiling concentration limit. As discussed and presented in greater detail elsewhere in this document, a charcoal tube method is recommended for personal sampling of airborne benzyl chloride. Gas chromatography is recommended for analyzing the adsorbed benzyl chloride.

(c) Medical Surveillance and Recordkeeping

Several reports of human [21,22,27,29,30] and animal [21,22,34] studies indicate that brief exposure to benzyl chloride vapor is sufficient to cause irritation of the eyes and respiratory tract. A medical surveillance program should include preplacement and periodic medical examinations that give particular attention to respiratory system, skin, and eyes. A preplacement chest roentgenogram and tests of forced vital capacity (FVC) and forced expiratory volume in the 1st second ($FEV_1$) are recommended to aid the physician in placement of workers with preexisting lung diseases

and to establish baseline values of pulmonary function. Periodic FVC and $FEV_1$ tests are recommended because benzyl chloride is a respiratory irritant that may increase airway resistance after long-term exposure. In addition, medical attention shall be provided for employees accidentally exposed to benzyl chloride. Medical records should be maintained for 30 years after termination of employment.

(d) Personal Protective Equipment and Clothing

Liquid benzyl chloride is reported to be a vesicant [27], and exposure to it could result in severe tissue damage [21,22,98]. Injection site necroses were reported in rats [55] and rabbits [40] given benzyl chloride sc in peanut oil or in gum tragacanth, respectively. Although no specific studies are known to have been conducted on its dermal absorption, benzyl chloride is lipophilic [3] and may be able to penetrate the skin. Benzyl chloride has been said to cause dermatitis [29].

No reports have been found concerning human sensitization to benzyl chloride, but Landsteiner and Jacobs [35] demonstrated the hypersensitivity of guinea pig skin to dermally applied liquid benzyl chloride subsequent to a series of intracutaneous injections of 0.01 mg benzyl chloride in saline solution.

Therefore, precautions must be taken to ensure adequate protection against dermal and mucosal contact with benzyl chloride. Personal protective equipment and clothing, including ocular protective devices and work clothes resistant to the penetration of and chemical action by benzyl chloride, should be available to and worn by workers in areas where exposure to benzyl chloride is likely. Showers and eyewash fountains must be available for immediate use in case of accidental contact.

(e) Informing Employees of Hazards

A continuing education program is an important part of a preventive hygiene program for employees who may be occupationally exposed to hazardous materials such as benzyl chloride. Properly trained persons should periodically apprise employees of possible sources of benzyl chloride exposure, the adverse health effects associated with such exposure, the engineering controls and work practices in use and being planned to limit exposure, and the environmental and medical monitoring procedures used to evaluate the effectiveness of control procedures. Employees should be informed of studies indicating a weak mutagenic potential in bacteria, of the report of tumors in rats injected repeatedly with high doses of benzyl chloride, and of the thorough scientific evaluation by NIOSH of the applicability of these data to the occupational environment. Employers may use other equally effective means for informing employees, such as health and safety booklets or the incorporation of health and safety instructions as integral parts of work protocols.

(f) Work Practices

Because benzyl chloride is a severe irritant and vesicant [27], it is recommended that eating, storing, handling, and dispensing of food be prohibited in areas where benzyl chloride is present. In addition, it is recommended that employees who work with benzyl chloride wash their hands thoroughly before eating, smoking, or using toilet facilities. Employees should be cautioned against touching or rubbing their eyes while working with benzyl chloride. In addition, appropriate work practices, training, and other protective measures should be required, regardless of the concentrations of benzyl chloride in the workplace environment.

(g) Engineering Controls

Engineering controls should be used whenever possible to maintain concentrations of airborne benzyl chloride within the recommended occupational exposure limits. In general, benzyl chloride should be contained in closed systems to prevent release of liquid or vapor to the environment. Exposure to benzyl chloride may be controlled by the use of respirators and protective clothing only during the time required to install adequate controls and equipment, to make process changes, to perform routine maintenance or repair operations, or during an emergency. Respirators should not be used as a substitute for appropriate engineering controls during normal operations.

(h) Monitoring and Recordkeeping Requirements

To ensure that workers are not exposed to benzyl chloride at concentrations which exceed the recommended environmental limit, concentrations in the workplace should be monitored at least annually and within 30 days of any process change likely to result in increased benzyl chloride concentrations. If the concentration of benzyl chloride in the work area exceeds the recommended ceiling limit, personal monitoring should be performed quarterly to ensure the adequacy of control procedures. If the results of personal sampling indicate benzyl chloride concentrations in excess of the recommended environmental limit, personal monitoring should be performed at least weekly and should continue until two consecutive determinations show that the workplace benzyl chloride levels no longer exceed the recommended limit. Quarterly monitoring may then be resumed. Records of environmental measurements should be retained for at least 30 years after employment ends.

# VII. RESEARCH NEEDS

Research is needed in the following areas to provide a better scientific basis for a recommended occupational health standard.

(a) Epidemiology

No epidemiologic study on employees working with benzyl chloride has been found; however, NIOSH is in the process of evaluating medical and personnel records obtained from a group of manufacturers to estimate the significance of any effects that may be identified. A retrospective cohort study of a working population exposed primarily to benzyl chloride for a sufficient time (20-30 years) should provide valuable information. Any epidemiologic study should also address the effects of alcohol consumption, smoking habits, and obesity on the assessment of occupational hazards and risks. There should be an attempt to identify a large population chronically exposed to benzyl chloride at low concentrations.

(b) Carcinogenicity

Two studies of the carcinogenic potential of benzyl chloride [55,56] have been reported. These involved ip injection of large doses into mice [56] and sc injection into rats [55]. However, these studies do not provide a substantive basis for quantitating the risk for human populations exposed to benzyl chloride at low concentrations throughout their working lifetimes. Properly designed and conducted studies should be performed on at least two mammalian species by the inhalation and dermal routes over a selected range of concentrations to further determine the risk of neoplastic disease. Also, studies to determine the cocarcinogenic or tumor-promoting potential of benzyl chloride should be performed.

(c) Mutagenicity

Two microbial studies [59,60] have indicated a mutagenic potential for benzyl chloride. However, potential mutagenic effects must be systematically investigated in greater detail with respect to dose, time, and route of exposure in both lower organisms and mammals. Animal tests using a variety of doses, schedules, and routes of administration should be performed to further elucidate any mutagenic potential.

(d) Teratogenicity and Related Reproductive Effects

There are no reported studies of teratogenic or related reproductive effects. Definitive experiments are needed with exposure concentrations approaching the recommended workplace environmental limit to determine the effects of low concentrations of airborne benzyl chloride on the reproductive processes in several mammalian species.

(e) Skin Effects

Benzyl chloride has been characterized as a vesicant. However, the data are incomplete and were mentioned secondarily in the reports. Additional information on the degree and character of skin effects on humans is highly desirable. In addition, long-term repetitive experiments should be performed to confirm the possibility of sensitization or other effects from benzyl chloride contact with the skin. Schedules and experimental designs similar to those used for inhalation studies should be followed.

(f) Long-term Animal Exposure Studies

Short-term animal exposure studies have been reported [21,22,34], but long-term experiments exposing several animal species to benzyl chloride vapor at a variety of concentrations approaching the recommended workplace environmental concentration limit are needed. These studies should simulate occupational exposure conditions of 8-10 hours/day, 4-5 days/week, for 18-24 months, and some of the animals should be maintained until the end of their natural lives. These studies should be properly designed and performed to permit assessment of general condition, biochemical/physiologic parameters, and gross and microscopic examinations of involved organs, including the liver, lungs, spleen, and kidneys and CNS and circulatory system.

Studies also are needed to determine the possible effects of DNA alkylation on rapidly dividing tissue, eg, intestine, bone marrow, and seminiferous tubules.

(g) Metabolism and Distribution

The pathways of metabolic transformation, distribution, and elimination of benzyl chloride as a function of the dose rate and route of administration in mammals and in humans have not been adequately investigated. Both in vivo and in vitro studies should be conducted to determine these pathways. The concentration at which saturation, if any, of the detoxification mechanisms occurs should be determined.

(h) Personal Protective Equipment

Lightweight materials, resistant to benzyl chloride penetration, should be identified for use in protective clothing, boots, gloves, and air-supplied hoods. Materials chemically resistant to benzyl chloride should be identified for use in waste containers, drainage channels, diversion dikes, and floors.

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# IX. APPENDIX I

## ANALYTICAL METHOD FOR BENZYL CHLORIDE

The following analytical method is an adaption of validated No. S-115, Physical and Chemical Analysis Branch of NIOSH [74].

### Principle of the Method

A known volume of air is drawn through a charcoal tube to trap the organic vapors present. The charcoal in the tube is transferred to a small, stoppered sample container, and the analyte is desorbed with carbon disulfide. An aliquot of the desorbed sample is injected into a gas chromatograph. The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

### Range and Sensitivity

The original analytical method, No. S-115, was validated over the range of 2-8 mg/cu m at an atmospheric temperature and pressure of 25 C and 744 mmHg, using a 10-liter sample. The probable range of the adapted method, under the conditions of sample size (3 liters), is 1.7-50 mg/cu m at a detector sensitivity that gives nearly full deflection on the strip chart recorder for a 0.05-mg sample. The method is capable of measuring much smaller amounts if the desorption efficiency (DE) is adequate. Desorption efficiency must be determined over the range used.

The upper limit of the range of the method is dependent on the adsorptive capacity of the charcoal tube. This capacity varies with the concentrations of the analyte and other substances in the air. The first section of the charcoal tube held at least 0.39 mg of the analyte when a test atmosphere of 8.1 mg/cu m of the analyte in dry air was sampled at 0.2 liter/minute for 4 hours. Breakthrough did not occur at this time; the concentration of the analyte in the effluent was less than 2% of that in the influent. (The charcoal tube consists of two sections of activated charcoal separated by a section of urethane foam. See Apparatus.) If a particular atmosphere is suspected of containing a large amount of contaminant, a smaller sampling volume should be taken.

### Interferences

When the amount of water in the air is so great that condensation actually occurs in the charcoal tube, organic vapors will not be trapped

efficiently. Preliminary experiments with toluene indicate that high humidity severely decreases the breakthrough volume.

When two or more compounds are known or suspected to be present in the air, such information, including their suspected identities, should be transmitted with the sample.

It must be emphasized that any compound that has the same retention time as the specific compound under study at the operating conditions described in this method is an interference. Retention time data on a single column cannot be considered as proof of chemical identity.

If the possibility of interference exists, separation conditions (column packing, temperature, etc) must be changed to circumvent the problem.

## Precision and Accuracy

Based on validation experiments using the internal standard method, the the coefficient of variation for the total analytical and sampling method No. S-115, in the range of 2-8 mg/cu m, was 0.096. This value corresponds to a standard deviation of 0.48 mg/cu m at the OSHA standard level of 5 mg/cu m as a TWA. The average values obtained using the overall sampling and analytical method were 6.3% less than the "true" value at the OSHA standard level. Precision and accuracy of the adapted method, which uses a reduced sample size of 3 liters, have not been measured.

The sampling device is small and portable and involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick instrumental method. The method also can be used for the simultaneous analysis of two or more compounds suspected to be present in the same sample by simply changing gas chromatographic conditions from isothermal to a temperature-programmed mode of operation.

One disadvantage of the method is that the amount of sample that can be taken is limited by the number of milligrams that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal tube exceeds 25% of that found on the front section, the possibility of sample loss exists.

Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the tubes. This drop will affect the flowrate and cause the volume to be imprecise because the pump is usually calibrated for one tube only.

Apparatus

(a) A calibrated personal sampling pump, the flow of which can be determined accurately (±5%) at the recommended flowrate.

(b) Charcoal tubes: glass tube with both ends flame sealed, 7 cm long with a 6-mm OD and a 4-mm ID, containing two sections of 20/40 mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The adsorbing section contains 100 mg of charcoal; the backup section, 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame ionization detector.

(d) Column (10-foot x 1/8-inch stainless steel) packed with 10% FFAP on 80/100 Chromosorb W-AW.

(e) An electronic integrator or some other suitable method of determining peak areas.

(f) Glass sample containers: 2-ml, with glass stoppers or Teflon-lined caps. If an automatic sample injector is used, the sample injector vials can be used.

(g) Microliter syringes: 10-µl and other convenient sizes for making standards.

(h) Pipets: 1.0-ml delivery type.

(i) Volumetric flasks: 10-ml or convenient sizes for making standard solutions.

Reagents

(a) Eluant: carbon disulfide (chromatographic grade).

(b) Benzyl chloride (reagent grade).

(c) Internal standard: n-heptadecane (99+%) or other suitable standard.

(d) n-Heptane (reagent grade).

(e) Purified nitrogen.

(f) Prepurified hydrogen.

(g) Filtered compressed air.

Procedure

(a) Cleaning of Equipment

All glassware used for the laboratory analysis should be washed with detergent and thoroughly rinsed with tapwater and distilled water.

(b) Calibration of Personal Pumps

Each personal pump must be calibrated with a representative charcoal tube in the line. This will minimize errors associated with uncertainties in the sample volume collected.

(c) Collection and Shipping of Samples

(1) Immediately before sampling, the ends of each tube should be broken to provide an opening at least one-half the internal diameter of the tube (2 mm).

(2) The smaller section of charcoal is used as a backup and should be positioned nearest the sampling pump.

(3) The charcoal tube should be placed in a vertical direction during sampling to minimize channeling through the charcoal.

(4) Air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

(5) A maximum sample size of 3 liters is recommended. Samples should be taken at a flow of 0.20 liter/minute or less. The flowrate should be known with an accuracy of at least ±5%.

(6) The temperature and pressure of the atmosphere being sampled should be recorded. If the pressure reading is not available, the elevation should be recorded.

(7) The charcoal tubes should be capped with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(8) One tube should be handled in the same manner as the sample tube (break, seal, and transport), except that no air is sampled through this tube. This tube should be labeled as a blank.

(9) Capped tubes should be packed tightly and padded before they are shipped to minimize tube breakage during shipping.

(10) A sample of the suspected compound should be submitted to the laboratory in glass containers with Teflon-lined caps. These liquid bulk samples should not be transported in the same container as the charcoal tubes.

(11) If samples must be stored before analysis, storage time should be minimal. Desorption efficiency has been shown to be unchanged after 7 days under unspecified conditions. Differences in storage temperature, water content, and other collected contaminants may, however, affect this time.

(d) Analysis of Samples

(1) Preparation of Samples

In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a 2-ml stoppered sample container or automatic sample injector vial. The separating section of foam is removed and discarded; the second section is transferred to another sample container or vial. These two sections are analyzed separately.

(2) Desorption of Samples

Prior to analysis, 1.0 ml of the eluant is pipetted into each sample container. For the internal standard method, a 0.2% solution of internal standard in carbon disulfide is used. Desorption should be done for 30 minutes. Tests indicate that this is adequate if the sample is agitated occasionally during this period. The sample vials should be capped as soon as the solvent is added to minimize volatilization.

> Extreme caution must be exercised at all times when using carbon disulfide because of its high toxicity and fire and explosion hazards. It can be ignited by hot steam pipes. All work with carbon disulfide must be performed under an exhaust hood.

(3) Gas Chromatograph Conditions

The typical operating conditions for the gas chromatograph are:

1. 30 ml/minute (80 psig) nitrogen carrier gas flow.
2. 30 ml/minute (50 psig) hydrogen gas flow to detector.
3. 300 ml/minute (50 psig) air flow to detector.
4. 170 C injector temperature.
5. 210 C manifold temperature (detector).
6. 160 C column temperature.

(4) Injection

The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, the solvent flush injection technique should be used. The 10-µl syringe is first flushed with solvent several times to wet the barrel and plunger, and 3 µl of solvent are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 µl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-µl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back 1.2 µl to minimize evaporation of the sample from the tip of the needle. (The sample occupies 4.9-5.0 µl in the barrel of the syringe.) Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

An automatic sample injector can be used if it is shown to give reproducibility at least as good as the solvent flush technique. In this case, 2-µl injections are satisfactory.

(5) Measurement of Area

The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below (see Calibration and Standards).

(e) Determination of Desorption Efficiency

(1) Importance of Determination

The DE of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process, provided that the same batch of charcoal is used.

(2) Procedure for Determination

Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 2-ml sample container. This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. A 12.5-mg/ml stock solution of the analyte in n-heptane is prepared. A known amount of this solution is injected directly into the activated charcoal with a 10-µl syringe, and the container is capped. The amount injected is equivalent to that present in a 10-liter sample at the selected level. It is not practical to inject the neat liquid directly because the amounts to be added would be too small to measure accurately.

At least six tubes at each of three levels (0.5X, 1X, and 2X the standard) are prepared in this manner and allowed to stand overnight to assure complete adsorption of the analyte onto the charcoal. These six tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described in Analysis of Samples.

The weight of analyte found in each tube is determined from the standard curve (see Calibration and Standards). Desorption efficiency is determined by the following equation:

$$DE = \frac{\text{average weight (mg) recovered}}{\text{weight (mg) added}}$$

The DE is dependent on the amount of analyte collected on the charcoal. Plot the DE vs the weight of analyte found. This curve is used below in Calculation (d) to correct for adsorption losses.

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/ml of carbon disulfide. (For the internal standard method, use carbon disulfide containing 0.2% of the internal standard.) A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas chromatographic conditions and during the same time as the unknown samples. Curves are established by plotting concentrations in mg/ml vs peak areas. In the case of the internal standard method, plot the concentration vs the ratio of peak area of analyte to peak area of internal standard.

Note: Whether the absolute area or the internal standard method is used, standard solutions should be analyzed at the same time that the

sample analysis is done. This will minimize the effect of variations of the flame ionization detector's response.

Calculations

(a) Read the weights, in mg, corresponding to each peak area from the standard curve. No volume corrections are needed because the standard curve is based on mg/ml eluant, and the volume of sample injected is identical to the volume of the standards injected.

(b) Corrections for the blank must be made for each sample.

$$mg = mg\ sample - mg\ blank$$

where:

mg sample = mg found in front section of sample tube
mg blank = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

(c) Add the weights present in the front and backup sections of the same sample tube to determine the total weight of the sample.

(d) Read the DE from the curve (Procedure (e)(2)) for the amount of analyte found in the front section. Divide the total weight by this DE to obtain the corrected mg/sample.

$$\text{corrected mg/sample} = \frac{\text{total weight}}{\text{DE}}$$

(e) The concentration of analyte in the air sampled can be expressed mg/cu m, which is numerically equal to g/liter of air.

$$\text{mg/cu m} = \frac{\text{corrected mg} \times 1{,}000\ (\text{liter/cu m})}{\text{air volume sampled (liter)}}$$

(f) Another method of expressing concentration is in ppm:

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{(T + 273)}{298}$$

where:

P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled
24.45 = molar volume (liter/mole) at 25 C and 760 mmHg
MW = molecular weight (g/mole) of analyte
760 = standard pressure (mmHg)
298 = standard temperature (K)

# X. APPENDIX II

## MATERIAL SAFETY DATA SHEET

The following items of information that are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation that appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances that are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, whereas a third component could be included both for its toxicity and its reactivity. Note that an MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid

using common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) that each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm $LC_{50}$-rat," "25 mg/kg $LD_{50}$-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a

permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest $LD_{50}$ if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, some irritation likely; prolonged or repeated contact, possibly strong irritation.

Eye Contact--some pain, transient irritation; corneal scarring if prolonged contact.

"Emergency and First-Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information that would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit, including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill," or "incineration." Warnings such as "comply with

local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or MSHA approval class, ie, "supplied air," etc. Protective equipment must be specified as to type and materials of construction.

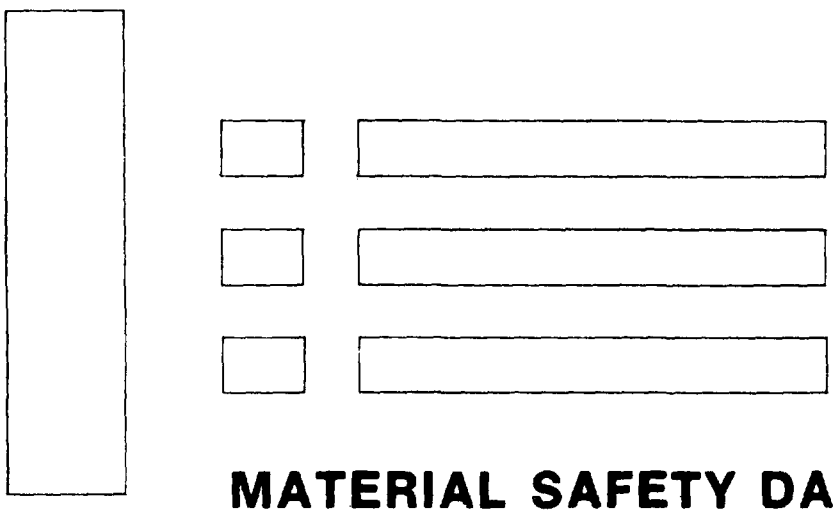
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific engineering control, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



# MATERIAL SAFETY DATA SHEET

| I PRODUCT IDENTIFICATION | |
|---|---|
| MANUFACTURER'S NAME | REGULAR TELEPHONE NO<br>EMERGENCY TELEPHONE NO |
| ADDRESS | |
| **TRADE NAME** | |
| **SYNONYMS** | |

| II HAZARDOUS INGREDIENTS | | |
|---|---|---|
| MATERIAL OR COMPONENT | % | HAZARD DATA |
| | | |
| | | |
| | | |
| | | |
| | | |
| | | |

| III PHYSICAL DATA | | |
|---|---|---|
| BOILING POINT 760 MM HG | | MELTING POINT |
| SPECIFIC GRAVITY ($H_2O$=1) | | VAPOR PRESSURE |
| VAPOR DENSITY (AIR=1) | | SOLUBILITY IN $H_2O$, % BY WT |
| % VOLATILES BY VOL | | EVAPORATION RATE (BUTYL ACETATE=1) |
| APPEARANCE AND ODOR | | |

## IV FIRE AND EXPLOSION DATA

| | | | |
|---|---|---|---|
| FLASH POINT (TEST METHOD) | | AUTOIGNITION TEMPERATURE | |
| FLAMMABLE LIMITS IN AIR, % BY VOL. | LOWER | | UPPER |
| EXTINGUISHING MEDIA | | | |
| SPECIAL FIRE FIGHTING PROCEDURES | | | |
| UNUSUAL FIRE AND EXPLOSION HAZARD | | | |

## V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

## VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

## VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

## VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

## IX SPECIAL PRECAUTIONS

PRECAUTIONARY
STATEMENTS

OTHER HANDLING AND
STORAGE REQUIREMENTS

PREPARED BY _____

ADDRESS _____

DATE _____

# XI. TABLES AND FIGURE

## TABLE XI-1

### CHEMICAL AND PHYSICAL PROPERTIES OF BENZYL CHLORIDE

| | |
|---|---|
| Molecular formula | $C_6H_5CH_2Cl$ |
| Molecular weight | 126.58 |
| Physical state | Liquid at normal temperatures |
| Color | Colorless to slightly yellow |
| Boiling point (760 mm) | 179.4 C (355 F) |
| Freezing point | -39.2 C (-38.6 F) |
| Flammable limits (lower limit) | 1.1% by vol in air |
| Flashpoint (closed cup) anhydrous | 67 C (153 F) |
| (open cup) anhydrous | 74 C (165 F) |
| Autoignition temperature | 585 C (1085 F) |
| Vapor Pressure 22 C | 1 mmHg |
| 60.8 C | 10 mmHg |
| 114.2 C | 100 mmHg |
| Specific gravity 25/25 C | 1.0986 |
| 20/20 C | 1.100 |
| Refractive index n15D | 1.541 |
| Solubility in water at 20 C (68 F) | 49.3 mg/100 ml |
| Miscibility | Decomposes in hot water; miscible in all proportions with alcohol, chloroform, ether |

Adapted from references 2,4,5,9,13,88,99

TABLE XI-2

OCCUPATIONS WITH POTENTIAL EXPOSURE TO BENZYL CHLORIDE

| | |
|---|---|
| Algicide makers | Gasoline additive workers |
| Benzyl alcohol workers | Germicide makers |
| Benzyl chloride workers | Motor fuel blenders |
| Benzyl ester makers | Perfume makers |
| Butyl benzyl phthalate workers | Pharmaceutical workers |
| Drug makers | Photographic developer makers |
| Dye intermediate makers | Quaternary ammonium compound workers |
| Dyemakers | Resin makers |
| Dyers | Rubber makers |
| Disinfectant makers | Tannin makers |
| Extreme pressure lubricant makers and users | Wetting-agent makers |
| Analytical chemists | Synthetic organic chemists |

Adapted from references 5,13,100

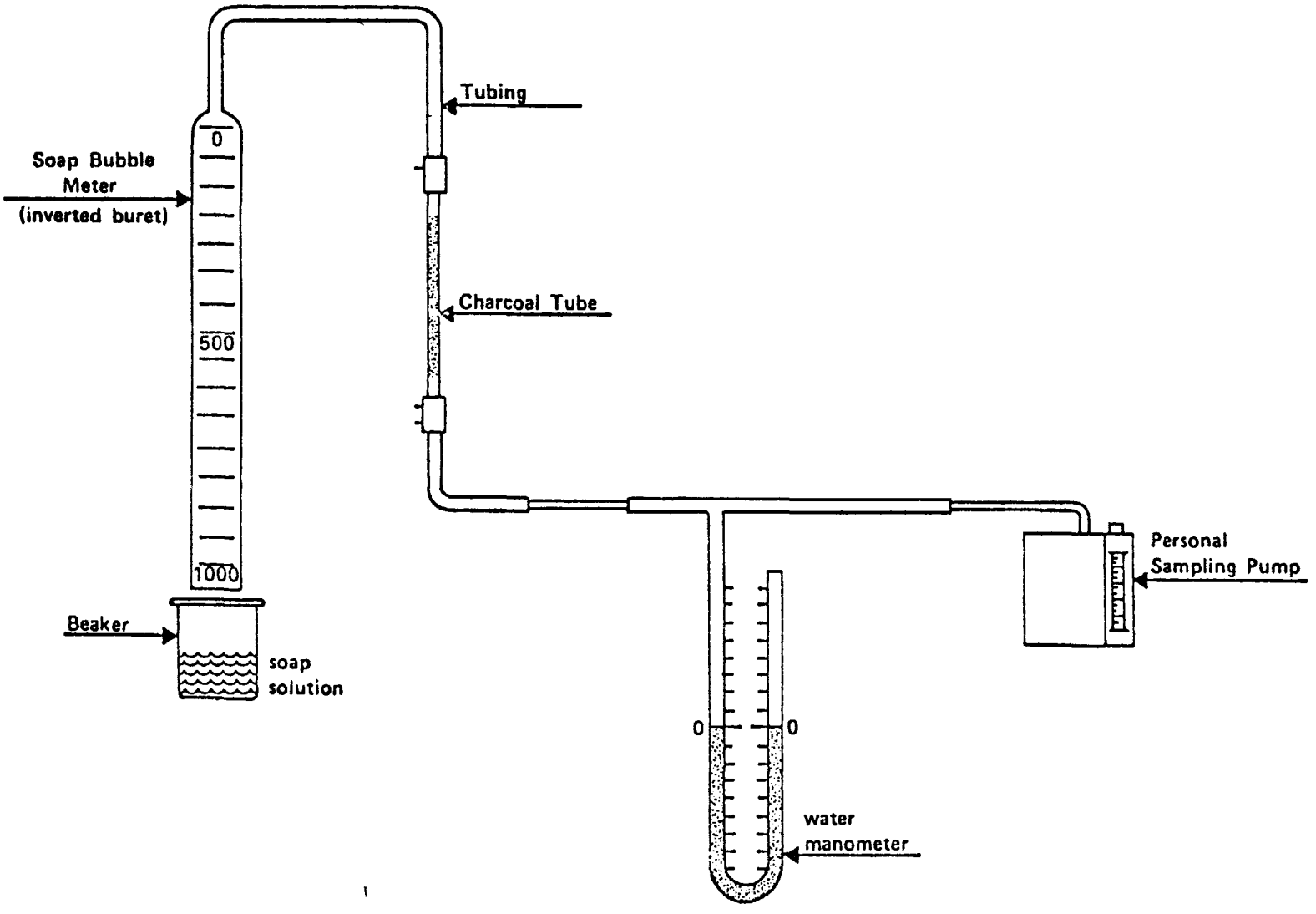



FIGURE XI -1. CALIBRATION SETUP FOR PERSONAL SAMPLING PUMP WITH CHARCOAL TUBE



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